UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

Mario Aliano, individually, and on behalf of all others similarly situated, Plaintiff, Jeff Worth and Robert Burns, Intervening Plaintiffs, v. CVS Pharmacy, Inc., a Rhode Island Corporation, Defendant.	Case No. 1:16-cv-02624-FB-MDG

REPRESENTATIVE PLAINTIFF'S POST-HEARING SUBMISSION IN SUPPORT OF HIS MOTION FOR PRELIMINARY APPROVAL OF CLASS ACTION SETTLEMENT AGREEMENT WITH CVS PHARMACY, INC.

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Proposed Settlement Class Counsel

This post-hearing submission will address some of the issues raised at the September 21, 2016 hearing on Plaintiff Mario Aliano's ("Plaintiff" or "Aliano") Motion for Preliminary Approval of the Class Settlement. For the sake of consistency and to avoid duplication, Plaintiff will expound on some of the issues raised at the hearing that were previously addressed in his Reply Brief, and Defendant will expound on some of the issues raised at the hearing that were previously addressed in its Reply Brief.

I. PLAINTIFF'S COUNSEL INVESTIGATED THE MEDICAL AND LEGAL ISSUES PRIOR TO FILING SUIT.

The *Worth* plaintiffs accuse Plaintiff's counsel, Thomas A. Zimmerman, Jr. ("Zimmerman"), of being inadequate Class Counsel based on their unsupported speculation that Zimmerman performed no investigation prior to filing the Aliano lawsuit. The *Worth* plaintiffs have no basis for that accusation. They are wrong.

On January 29, 2016, the class settlement was announced in *Jovel, et al. v. i-Health, Inc.*, No. 12-cv-05614 (the "Jovel Action"), and a motion for preliminary approval of the class settlement was filed in the Jovel Action. Upon learning of that settlement, Zimmerman began investigating a potential claim against CVS on behalf of Aliano, who had been taking a companion Algal-900 DHA product on several occasions for approximately one (1) year prior thereto. *See* Declaration of Mario Aliano ("Aliano Decl.") ¶¶ 3-6, attached as Exhibit 1 to Plaintiff's Reply in Support of the Motion for Preliminary Approval.

As part of that investigation, Zimmerman consulted with Bruce Livingston, D.O. Dr. Livingston has been a physician for over 35 years. He also graduated from law school, and passed the Illinois Bar Exam in 1989. Since 1990, he owns and operates MedWitness, Ltd., where he serves as a medical consultant to attorneys in legal matters. *See* Bruce Livingston, D.O. Declaration ("Livingston Decl.") ¶ 1, attached hereto as Exhibit A.

As a medical-legal consultant over the past 25 years, Dr. Livingston routinely researches and reviews medical literature and scientific studies in an effort to determine the validity of medical and other claims that are being asserted in legal matters. His education and experience as a physician, in conjunction with his legal training, gives him a unique insight and ability to assimilate medical and legal issues and render opinions to assist attorneys in their legal matters. *See* Livingston Decl. ¶ 2, Exhibit A.

During the first week of February 2016, Zimmerman spoke to Dr. Livingston about the CVS Algal-900 DHA product. DHA, the primary ingredient in Algal-900, is a type of Omega-3 fatty acid. Zimmerman told Dr. Livingston that he and his firm were researching certain issues because they were considering filing a lawsuit against CVS. Zimmerman asked Dr. Livingston whether DHA or Omega-3 fatty acids were "clinically shown" to improve adult memory function, or whether that would be a false and misleading representation on the CVS product. Zimmerman provided Dr. Livingston with a photograph of the Algal-900 product packaging on which it stated that the product was "clinically shown to improve memory". *See* Livingston Decl. ¶ 3, Exhibit A.

Dr. Livingston knew the health benefits of DHA from his medical education and experience. In addition, Dr. Livingston researched the medical and scientific literature and other related documents, including the "MIDAS Study", the FTC Decision and Order in *In the Matter of i-Health, Inc. and Martek Biosciences Corp.*, and the Dissenting FTC Commissioner's opinion in the *i-Health* matter. *See* Livingston Decl. ¶ 4, Exhibit A.

Dr. Livingston told Zimmerman his opinion that DHA and Omega-3 fatty acids were not "clinically shown" to improve adult memory function, that he disagreed with the dissenting FTC Commissioner's opinion, and that the representation on the Algal-900 product packaging would give rise to a medically-based legal claim against CVS. Zimmerman and his firm filed the

Aliano lawsuit against CVS after Dr. Livingston conveyed his opinion to Zimmerman. *See* Livingston Decl. ¶ 5, Exhibit A.

Prior to filing suit, Zimmerman consulted with an experienced physician who also went to law school and passed the Illinois Bar Exam, and whose primary business for the past 25 years is consulting with attorneys on medical-legal issues. Zimmerman consulted with Dr. Livingston in an effort to determine whether DHA and Omega-3 fatty acids were "clinically shown" to improve adult memory function, or whether that representation on the Algal-900 product packaging would give rise to a medically-based legal claim against CVS.

This is exactly the type of investigation that should be performed prior to filing a lawsuit.

The *Worth* plaintiffs' accusation that Zimmerman did not perform any investigation prior to filing suit is baseless.

II. PLAINTIFF'S COUNSEL INVESTIGATED THE MERITS OF THE "PURE DHA MEMORY SUPPORT" CLAIM PRIOR TO AGREEING THAT IT WOULD NOT VIOLATE THE INJUNCTION.

The *Worth* plaintiffs also accuse Zimmerman of being inadequate Class Counsel based on their unsupported assertion that Zimmerman performed no investigation prior to agreeing that the inclusion of the new phrase "pure DHA memory support" on the new Algal-900 product packaging does not violate the injunction in the settlement agreement. *See* Amended Stipulation of Settlement, ¶ 3.3. Again, the *Worth* plaintiffs are wrong.

When counsel for Aliano was discussing settlement with Defendant's counsel in April 2016, the subject of the new phrase "pure DHA memory support" on the new Algal-900 product packaging was discussed, as the new product packaging had already been in commercial use for several months. In order to investigate what, if any, implications that new phrase would have on a settlement in this case, Sharon Harris ("Harris"), an attorney at Zimmerman Law Offices, discussed that issue with Carol L. Henricks, M.D. Dr. Henricks is a licensed physician

specializing in neurology, and brain science has been a focus of her education and training. *See* Declaration of Carol L. Henricks, M.D. ("Henricks Decl.") ¶ 1, attached hereto as Exhibit B.

In 1991, Dr. Henricks received her M.D. degree from Hahnemann University School of Medicine. Thereafter, she performed her neurology residency at Hahnemann University Hospital, where she served as Chief Resident in neurology. Following her residency, Dr. Henricks performed a Fellowship in clinical neurophysiology at the University of Michigan. After that, she performed a second Fellowship in behavioral neurology and memory disorders at the University of Arizona. *See* Henricks Decl. ¶ 2, Exhibit B.

After completing her second Fellowship, Dr. Henricks went into private practice as a specialist in neurology. She has been in private practice for the past 18 years. *See* Henricks Decl. ¶ 3, Exhibit B.

Dr. Henricks participated in several research projects involving memory function. She was a research assistant in memory studies at Yale University and the University of Pittsburgh Learning Research and Development Center, and she conducted research on the clinical neurophysiology of learning and memory during medical school. *See* Henricks Decl. ¶ 4, Exhibit B.

In early April 2016, Harris spoke to Dr. Henricks in connection with settlement discussions that Zimmerman Law Offices was having with counsel for CVS relative to the Aliano case. They talked about docosahexaenoic acid (DHA), which is an omega-3 fatty acid that is a primary structural component of the human brain and cerebral cortex, among other things. *See* Henricks Decl. ¶ 5, Exhibit B.

Dr. Henricks noted that it is well-established in medicine that DHA promotes normal brain development and cognitive function, and that taking dietary DHA supplements is

associated with the maintenance of normal brain and cognitive functions, such as memory and learning abilities. *See* Henricks Decl. ¶ 6, Exhibit B.

During those discussions, Harris asked whether the phrase "pure DHA memory support" would be supported by the relationship between DHA and brain health. Dr. Henricks told Harris her opinion is that taking dietary DHA supplements supports brain development, cognitive function, and memory. Dr. Henricks' opinion was based on her training, education, research and experience, and her review of reliable medical and scientific studies. *See* Henricks Decl. ¶ 7, Exhibit B.

Again, this is exactly the type of investigation that should be performed when dealing with medical issues in a legal case. Dr. Henricks is a highly-experienced neurologist who specializes in brain development and memory function, and who has participated in several research projects involving memory function.

Zimmerman agreed that the new phrase "pure DHA memory support" on the new Algal-900 product packaging would not violate the injunction in the settlement agreement after Dr. Henricks conveyed her opinion to Harris.

The *Worth* plaintiffs' accusation that Zimmerman did not perform any investigation prior to agreeing to this settlement term is baseless.

Mario Aliano, individually, and on behalf of all others similarly situated,

By: /s/ Thomas A. Zimmerman, Jr.

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Proposed Class Counsel and Counsel for the Plaintiff

CERTIFICATE OF SERVICE

Thomas A. Zimmerman, Jr., an attorney, hereby certifies that he caused the above and foregoing *Post-Hearing Submission* to be served upon counsel of record in this case via the U.S. District Court CM/ECF System, on this day September 28, 2016.

s/Thomas A. Zimmerman, Jr.

BRUCE LIVINGSTON, D.O. DECLARATION

I, Bruce Livingston, D.O., hereby state and declare as follows:

1. I have been a physician for over 35 years. I also graduated from law school, and passed the Illinois Bar Exam in 1989. Since 1990, I own and operate MedWitness, Ltd., where I serve as a medical consultant to attorneys in legal matters. See attached *CV*.

2. As a medical-legal consultant over the past 25 years, I routinely research and review medical literature and scientific studies in an effort to determine the validity of medical and other claims that are being asserted in legal matters. My education and experience as a physician, in conjunction with my legal training, gives me a unique insight and ability to assimilate medical and legal issues and render opinions to assist attorneys in their legal matters.

3. During the first week of February 2016, Tom Zimmerman, an attorney at Zimmerman Law Offices, PC, spoke to me about an issue that he was investigating relative to the CVS Algal-900 DHA dietary supplement product. DHA, the primary ingredient in Algal-900, is a type of Omega-3 fatty acid. Mr. Zimmerman told me that he and his firm were researching certain issues because they were considering filing a lawsuit against CVS. He asked me whether DHA or Omega-3 fatty acids were "clinically shown" to improve adult memory function, or whether that would be a false and misleading representation on the CVS product. Mr. Zimmerman provided me with a photograph of the Algal-900 product packaging on which it stated that the product was "clinically shown to improve memory".

4. I knew the health benefits of DHA from my medical education and experience. In addition, I researched the medical and scientific literature and other related documents, including:

   a. The "MIDAS Study" – Karin Yurko-Mauro, *Beneficial Effects of Docosahexaenoic Acid on Cognition in Age-Related Cognitive Decline*, 6 *Alzheimer's & Dementia* 456 (2010).

   b. FTC Decision and Order: *In the Matter of i-Health, Inc. and Martek Biosciences Corp.*, No. C-4486 (August 21, 2014).

   c. FTC, *Statement of Chairwoman Edith Ramirez and Commissioner Julie Brill: In the Matter of i-Health, Inc. and Martek Biosciences Corp.*, No. C-4486 (June 6, 2014).

EXHIBIT A

d. FTC, *Separate Statement of Commissioner Maureen K. Ohlhausen, Dissenting in Part: In the Matter of i-Health, Inc. and Martek Biosciences Corp.*, No. C-4486 (June 5, 2014).

e. U.S. National Institutes of Health, *Omega-3 Fatty Acids and Health: Fact Sheet for Health Professionals* (2005).

f. Jiangjian Jiao et al., *Effect of n-3 PUFA Supplementation on Cognitive Function Throughout the Life Span from Infancy to Old Age: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*, Am. J. Clinical Nutrition (2014).

g. Emily Y. Chew et al., *Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function*, 314 JAMA 791 (2015).

h. Catherine H. MacLean, et al., *Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases*, National Center for Biotechnology Information.

5. I told Mr. Zimmerman my opinion that DHA and Omega-3 fatty acids were not "clinically shown" to improve adult memory function, that I disagreed with the dissenting FTC Commissioner's opinion, and that the representation on the Algal-900 product packaging would give rise to a medically based legal claim against CVS. Mr. Zimmerman and his firm filed a lawsuit against CVS after I conveyed my opinion to him.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge, information and belief.

Dated: September 27, 2016.

Bruce Livingston, D.O.

BRUCE LIVINGSTON, D.O., J.D.

- CURRICULUM VITAE -

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1968-70	Loyola University - Chicago
1970-72	Illinois Institute of Technology (B.S. Biology)
1972-73	Illinois College of Podiatric Medicine
1973-77	Chicago College of Osteopathic Medicine (D.O.)
1977-78	Chicago Osteopathic Hospitals & Clinics (rotating internship)
1977	FLEX EXAM, National licensing examination for M.D.s, passed
1978	Osteopathic National Board Examinations for D.O.s, passed
1978-87	Family Practice - private practitioner and director (primary care medicine & outpatient/ambulatory orthopedics), Chicago, Il.
1979-85	Police Surgeon - City of Palos Hills, IL.
1981-83	Instructor, Chicago College of Osteopathic Medicine (Chemistry)
1981-84	Medical Consultant - Sheriff's Office of Cook County.
1985-89	John Marshall Law School, Chicago (J.D.)
1989	Illinois Bar Exam, passed
1990-present	Owner -MedWitness, Ltd. (Medical expert witness consultants)
2005-	President- Livingston Medical Group, Chartered. (Disability. Ins. Rev.)
2010	Northwestern University, Kellogg School of Management (AEP. Cert)
2010	MedClaim Informatics, L.L.C. (Medical Analysis of Injury Claims)
2014	DEA Seminar on controlled substances - Palos Hills, IL
2016	Certified in surgical Probuphine insertion/removal, Chicago, IL.

ELSEVIER

Alzheimer's & Dementia 6 (2010) 456–464

Alzheimer's & Dementia

Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline

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Abstract

Background: Docosahexaenoic acid (DHA) plays an important role in neural function. Decreases in plasma DHA are associated with cognitive decline in healthy elderly adults and in patients with Alzheimer's disease. Higher DHA intake is inversely correlated with relative risk of Alzheimer's disease. The potential benefits of DHA supplementation in age-related cognitive decline (ARCD) have not been fully examined.

Objective: Determine effects of DHA administration on improving cognitive functions in healthy older adults with ARCD.

Methods: Randomized, double-blind, placebo-controlled, clinical study was conducted at 19 U.S. clinical sites. A total of 485 healthy subjects, aged $\geq$55 with Mini-Mental State Examination >26 and a Logical Memory (Wechsler Memory Scale III) baseline score $\geq$1 standard deviation below younger adults, were randomly assigned to 900 mg/d of DHA orally or matching placebo for 24 weeks. The primary outcome was the CANTAB Paired Associate Learning (PAL), a visuospatial learning and episodic memory test.

Results: Intention-to-treat analysis demonstrated significantly fewer PAL six pattern errors with DHA versus placebo at 24 weeks (difference score, -1.63 ± 0.76 [-3.1, -0.14, 95% CI], $P = .03$). DHA supplementation was also associated with improved immediate and delayed Verbal Recognition Memory scores ($P < .02$), but not working memory or executive function tests. Plasma DHA levels doubled and correlated with improved PAL scores ($P < .02$) in the DHA group. DHA was well tolerated with no reported treatment-related serious adverse events.

Conclusions: Twenty-four week supplementation with 900 mg/d DHA improved learning and memory function in ARCD and is a beneficial supplement that supports cognitive health with aging.

Trial Registration: Clinicaltrials.gov, Identifier: NCT0027813.

Keywords: cognition; memory; learning; aging; omega-3 fatty acid; docosahexaenoic acid; clinical trial; nutrition

Conflicts of Interest Disclosure: With the exception of Drs. Dror Rom, Andrew Blackwell, and Mary Stedman, the other authors are employed by Martek Biosciences Corporation. Dr. Rom and Dr. Blackwell were consultants to the study. The participating clinical investigators are listed as a group in the acknowledgement section of the manuscript.

Contributors: Blackwell, Nelson, Rom, Yurko-Mauro contributed to the study concept and design. Blackwell, McCarthy, Nelson, Rom, Yurko-Mauro and Stedman participated in study conduct and collection of the data. Rom had responsibility for the statistical analysis. Blackwell, Nelson, Rom, Ryan, Salem, Yurko-Mauro contributed to the interpretation of data. Blackwell, Ryan, Yurko-Mauro contributed to the drafting of the manuscript and McCarthy, Nelson, Rom, Ryan, Salem, Stedman and Yurko-Mauro participated in the revision of the manuscript. The corresponding author had full access to all data in the study after study unblinding, and had final responsibility for the writing of the report and the decision to submit for publication. The study was funded by Martek Biosciences Corporation.

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1. Introduction

A decline in memory and cognitive function is considered to be a normal consequence of aging. Memory loss is a prominent health concern, second only to heart disease for older individuals [1]. Prevalence estimates indicate that as many as 5.4 million older Americans (22.2%) have cognitive impairment without dementia. Approximately 12% of these elders will develop dementia annually [2]. Docosahexaenoic acid (DHA) is the principle long-chain polyunsaturated fatty acid (LCPUFA) in brain. Several epidemiological studies associate decreases in plasma DHA with cognitive decline in healthy elderly people [3,4] and in patients with Alzheimer's disease (AD) [5,6]. Populations with high dietary intake of DHA [7–9] and greater plasma DHA levels [4,6] have a lower risk of cognitive impairment or AD.

As an integral component of neural membrane phospholipid, DHA constitutes 30%–40% of LCPUFAs in grey matter cerebral cortex [10]. DHA is involved in multiple brain functions including cell membrane fluidity, receptor affinity, and modulation of signal transduction molecules [11]. In preclinical studies, DHA supplementation restored brain DHA levels and long-term potentiation [12], improved cerebral blood flow [13], and enhanced learning and memory tasks in aged animals [14]. DHA also reduced beta amyloid, plaque burden, and tau protein in transgenic AD models [15,16].

Clinical trials with LCPUFAs from fish oil (containing a mixture of eicosapentaenoic acid (EPA) and DHA) in healthy older adults or individuals with mild cognitive impairment (MCI) or AD have been conducted. No studies with DHA alone have investigated mild, age-associated cognitive changes (i.e., age-related cognitive decline, ARCD). A recent study of 302 elders with Mini-Mental State Examination (MMSE) scores >21, supplemented for 6 months with 400 or 1800 mg/d of DHA + EPA versus placebo, showed no significant changes on cognitive tests [17]. A small pilot study showed significant improvements in the Alzheimer Disease Assessment Scale cognitive subscale (ADAS-cog) in subjects with MCI but not in AD patients given 1.8 g/d DHA + EPA for 6 months versus placebo [18]. A trial of 204 mild to moderate AD patients showed no delay in rate of decline on ADAS-cog with DHA + EPA (2.3 g/d) administration [19]. However, in a sub-group of individuals with MMSE scores >27, there was a significant decrease in the MMSE rate of decline after 6 and 12 months supplementation. These results suggest that older adults with mild cognitive deficits may benefit the most from LCPUFAs.

We examined the potential benefits of 900 mg/d DHA on cognitive changes in individuals with ARCD in this double-blind, randomized, placebo-controlled, multi-center clinical trial, using the Cambridge Neuropsychological Test Automated Battery, CANTAB. The CANTAB cognitive battery is a validated, reliable neuropsychological battery [20], which consists of memory, learning, attention, problem-solving, and executive function tests [21]. Its measures of visuospatial associative learning demonstrate specificity and sensitivity in detecting isolated memory impairments in healthy older adults [22,23]. It was hypothesized that 24 weeks of DHA supplementation would improve cognitive function as assessed by the CANTAB Paired Associate Learning (PAL) test, a learning and episodic memory test. The PAL test was chosen as the primary endpoint because it uses mnemonic processes of the medial temporal lobe, a region where some of the earliest cognitive and neuronal dysfunctions are detected during aging and in pre-dementia conditions [24,25]. Collectively, these studies demonstrate PAL's sensitivity to early visuospatial learning and memory changes which may be affected by DHA.

2. Methods

2.1. Participants

A total of 485 male or female subjects, aged ≥55 years with a subjective memory complaint and who met criteria for ARCD were enrolled at 19 sites in the United States. The Diagnostics and Statistical Manual (DSM IV) defines ARCD as an ''objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given a person's age. Individuals may report problems remembering names or appointments or may experience difficulty solving complex problems.'' [26] A similar term, ''age-associated memory impairment'' has been used to describe specifically age-related memory loss [27]. We chose the DSM IV term ''age-related cognitive decline'' because of its acceptability as a standard, codified, diagnostic classification and broader definition encompassing cognitive function.

The Logical Memory sub-test of the Wechsler Memory Scale (WMS version III, 1997) was used to identify objectively individuals with a decline in cognitive function who had a baseline raw (immediate or delayed recall) score ≥1 standard deviation (SD) below the mean of younger adults (reference ages, 25–35 years). The cut-offs used for inclusion in the study were ≤28 for the Logical Memory immediate recall or ≤15 for the delayed recall score. Subjects were excluded if they had an MMSE score <26. To minimize the potential confounding effect of high DHA consumption before study entry, subjects who consumed >200 mg/d DHA in 2 months before randomization (determined by a DHA food frequency questionnaire [FFQ]) [28], or consumed omega-3 containing supplements, or used medications for AD, major antipsychotics, or anti-depressants were excluded from the study. A history or presence of major medical conditions (including a diagnosis of dementia or a Geriatric Depression score >5), and current or past alcohol or drug abuse also excluded subjects from eligibility. Institutional review board (New England IRB) approval was obtained, and all subjects provided written informed consent.

2.2. Procedures

The study consisted of a screening visit, followed 1 week later by a baseline visit, and three follow-up visits. Safety and

compliance measures were assessed at every visit. Efficacy assessments were obtained at baseline, week 12, and week 24. Eligible subjects were stratified by age (55–69; ≥70) and randomized 1:1 in blocks of four to active or placebo by site, using a centralized interactive voice randomization system (Fisher Clinical, FACTS services, Allentown, PA).

Subjects allocated to active treatment received 900 mg/d DHA, provided as (3) soft-gelatin capsules, each containing 300 mg DHA from algal triglyceride oil (DHA-S single cell oil from *Schizochytrium sp*, containing 40% DHA, ≤1% EPA, 15% docosapentaenoic acid [DPAn-6], plus antioxidants: 320 μg ascorbyl palmitate [8 IU ascorbic acid], 1.6 mg mixed tocopherols [7 IU d-α-tocopherol], and 2000 ppm rosemary extract). The 900 mg dose was chosen because cumulative cross-study dose response data demonstrated doubling in plasma DHA levels [29] and positive changes in cardiovascular lipid profiles [30]. DHA-S oil is a nutritional food ingredient that is Generally Recognized as Safe, GRAS Review Notification (GRN 137) [31], and manufactured under food Good Manufacturing Practice conditions. Placebo capsules were identical in size and appearance and consisted of 50% corn oil/50% soy oil, and the same antioxidant mixture. All capsules were orange-flavored and orange color to protect the study blind. Subjects were instructed to take capsules with food at the same time each day (e.g., 1 capsule/meal), starting at the baseline visit, and to not alter their normal diet during the study. The DHA FFQ was administered to assess ongoing dietary intake of LCPUFA and subject compliance. The primary measure of compliance was the week 24 change from baseline plasma phospholipid DHA level. A change greater than 1.5 wt% (based on historical dose response plasma DHA levels) was considered compliant for the DHA group. Capsule counts were conducted at each site visit and served as a secondary measure of compliance.

2.3. Outcome measures

The primary outcome was a week 24 change from baseline in the CANTAB PAL, a visuospatial learning and episodic memory test [22]. The test battery is computer based using a touchtone screen. A pre-baseline training session with CANTAB was conducted at screening to familiarize the subject with the computer battery and to minimize learning effects at subsequent test sessions. These data were not analyzed. The order of test sequence remained constant across all test sessions. Parallel versions of most tests were used at subsequent test sessions to minimize any potential ceiling effects. The following test variants were used: Pre-baseline Parallel version 1; Baseline = Parallel Version 2, Week 12 = Parallel Version 3, Week 24 = Parallel Version 4. All CANTAB data were collected electronically, processed, and validated by Cambridge Cognition Ltd. Final data sets were transferred to Prosoft Software, Inc. (Wayne, PA) for statistical analysis. The Wechsler Logical Memory test, used in screening, was not chosen as an outcome measure because it is not available in a computerized format and does not have parallel versions. These criteria are especially desirable in a large, multicenter clinical trial because they minimize potential bias and variability.

Secondary outcome measures included CANTAB Pattern Recognition Memory (PRM), a test of visual pattern recognition administered as a 2-choice forced discrimination series; CANTAB Verbal Recognition Memory (VRM), a test of immediate and delayed verbal memory; CANTAB Stockings of Cambridge (SOC), a test of executive function; and CANTAB Spatial Working Memory (SWM), a test of temporary spatial retention and search strategy. Other secondary measures included self-assessment tests of memory (Frequency of Forgetting-10 scale [32]) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Prevention Instrument (ADCS-ADL PI scale) [33], MMSE [34], and the Geriatric Depression scale [35].

Safety assessments included adverse event monitoring, changes in vital signs, and physical examinations. Chemistry, hematology, and urinalysis tests were also conducted. Nonfasting blood samples were collected at baseline and at week 24. Plasma phospholipid fatty acids were analyzed as described previously [36]. APOE genotyping was not done.

2.4. Statistical analysis

The primary efficacy analysis was determined a priori and based on a linear univariate model of the change from baseline in the PAL 6 pattern error score at 24 weeks using treatment, site, age group (55–69 and ≥70 years), and education as factors, and the baseline PAL score as a covariate. The calculated effect size for the PAL was 0.19. The study was not designed to look at a rate of change in cognition over time. The primary efficacy analysis was tested in the intention-to-treat (ITT) population defined as all randomized subjects who received study treatment and had baseline evaluations. Planned per protocol analyses were also conducted. Levene's test examined homogeneity of variance across groups. All efficacy analyses used the ''Last Observation Carried Forward'' (LOCF) approach for handling missing data. Planned secondary efficacy analyses followed the method of the primary analysis. Safety analyses also used an analysis of covariance model or Fisher's Exact Test to assess treatment differences. A 2-fold increase in plasma phospholipid DHA levels was expected with 900 mg/d, based on previous dose response data [29].

A preplanned interim analysis (IA) for futility was conducted by an unblinded statistician not associated with data collection after 140 subjects completed the study. The objective of the early IA was to allow us to terminate the study if no efficacy was demonstrated. Preplanned conditional power calculations revealed a conditional power of 30% and indicated sample size adjustment based on imputed PAL error adjustments which overestimated total errors and increased variability. The planned interim look at a co-primary endpoint, PRM did not meet the conditional power threshold of 20%–30% and was thus specified as a secondary endpoint

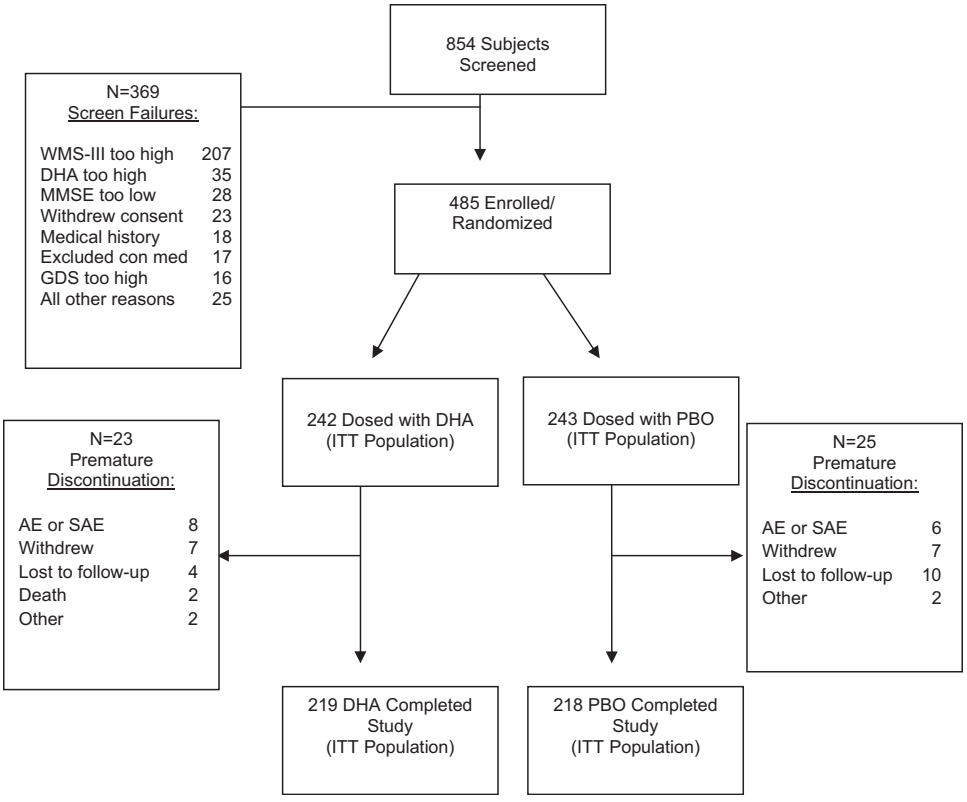

Fig. 1. Participant flow. Abbreviations: WMS, Wechsler Memory Scale; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

in the final analysis plan. For 80% (conditional) power, using the PAL 6 pattern error score (two-sided $P < .05$), a sample size of 325 subjects, post-IA was needed with 10% drop out rate calculated. All analyses were performed using SAS software, version 8.2.

3. Results

A total of 854 subjects were screened for the study, 369 subjects failed screening, and 485 subjects met study criteria and were randomized to DHA (242 subjects, ITT) or placebo (243 subjects) (Fig. 1). Of the subjects who failed screening, 56% did not meet the Logical Memory test criteria for ARCD. Only 9% of screen failures had elevated, disqualifying baseline DHA intake levels. All subjects received the correct treatment to which they were randomized. An overall study completion rate of 90% was achieved (219 subjects, DHA; 218 subjects, placebo). Baseline characteristics, including age, gender, race, education, and medication use (Table 1), showed no significant differences between groups.

3.1. Primary outcome

After 24 weeks, individuals in the DHA group had significantly fewer PAL 6 pattern errors (ITT difference score, -1.63 ± 0.76 (-3.1, -0.14, 95% CI), $P = .032$) compared with the placebo group (Table 2). There were no significant differences between groups on the PAL and other CANTAB tests at week 12 (data not shown). The per protocol ($P = .025$) analyses resulted in similar significant findings for PAL. The PAL data demonstrated homogeneity of variance across groups (Levene's test, $P = .58$), post hoc analysis of the univariate model without the cofactors age and education also showed a significant DHA response ($P = .029$), and an analysis using observed cases only displayed the same directional trend ($P = .067$).

The Logical Memory delayed recall score, as a covariate, was highly predictive of the change in PAL errors within the DHA group at week 24 ($r = -.36$, $P < .001$). Thus, worse baseline delayed recall scores were associated with greater improvement in PAL scores with DHA. Adjusting for the delayed recall score strengthened the DHA treatment effect (diff score, -1.73 ± 0.77, $P = .026$). Family history of dementia ($P = .054$) and concomitant statin medication use ($P = .049$, per protocol) were also predictive of the change in PAL within the DHA group. Other covariates (education, site, and age group) were not significant, although the older stratified group (age, ≥ 70) made more PAL errors than the younger group (55–69 years). The PAL treatment response was not analyzed by gender.

CANTAB has collected age-associated PAL normative cross-sectional data for individuals 55–93 years of age from several studies (*www.camcog.com*). Using these data as a frame of reference, at baseline, the PAL error performance data for the DHA group corresponded to a cognitive age of 72.6 years. After 24 weeks of supplementation, the

Table 1
Baseline characteristics

Parameter	DHA (n = 242)	Placebo (n = 243)	*P* value*
Gender (%)	44 M; 56 F	40 M; 60 F	.42
Age (±SD)	70 (9.3)	70 (8.7)	.98
Education years (±SD)	14.5 (2.5)	14.7 (2.6)	.80
Race (%)			.88
African-American	7	7	
Asian	.8	1.2	
White, non-Hispanic	85	83	
White, Hispanic	5	7	
Native American	1.2	0.4	
Baseline DHA intake mg/d (±SD)	103.5 (53.6)	104.7 (49.4)	nd
Alcohol consumption U/wk (±SD)	2.18 (3.4)	2.41 (3.7)	.37
Family history of dementia n (%)	83 (34)	93 (38)	.60
Logical memory, immediate recall mean (±SD)	25 (6.8)	25.1 (6.9)	.82
Logical memory, delayed recall mean (±SD)	11.3 (4.1)	11.2 (4.1)	.51
Statin use (%)	36	37	nd
Lipophilic statins	95	86	
Antihypertensive use (%)			nd
Diuretics	20	24	
Ace-inhibitors	15	14	
Ca^{++} channel blockers	9	9	
β-blockers	5	3	

Abbreviation: nd, not done.

*Based on an ANOVA model with effects treatment and pooled site for continuous parameters; or for categorical parameters, a Cochran-Mantel-Haenszel test for associations adjusting for pooled site.

cognitive age represented by the PAL scores was 65.6 years of age, indicating a 7 year improvement in PAL scores. In comparison, the PAL error performance scores for the placebo group at baseline corresponded to 70.6 years and 66.9 years at week 24, only a 3.6 year improvement. The CANTAB normative data provide, for illustrative purposes, a frame of reference comparing the magnitude of the changes in performance observed with DHA to the changes in performance that one could expect to see over time in the course of normal aging. When interpreting the positive cognitive effects associated with DHA, it should be kept in mind that the cited CANTAB norms are based on age-stratified, cross-sectional rather than longitudinal data.

3.2. Secondary outcomes

Additional CANTAB tests and other cognitive measures are also shown in Table 2. CANTAB VRM test showed significant week 24 change from baseline total immediate and delayed responses with DHA supplementation versus placebo. The baseline VRM delayed score was highly predictive and inversely associated with DHA treatment response ($r = -.52$, $P < .001$). At week 24, compared to baseline, PRM and SWM tests were not significantly different between groups. On CANTAB SOC, the placebo group demonstrated small, significant week 24 differences in the number of problems solved.

There were no significant differences in change from baseline scores on the MMSE, the Geriatric Depression scale (Table 2), or Frequency of Forgetting scale (mean change from baseline, DHA = 1.6 ± .5; placebo = 2.8 ± 0.5, $P < .12$), and the ADCS-ADL PI scale (mean change from baseline, DHA = −2 ± 0.3; placebo = −1.7 ± 0.3, $P < .59$). Dietary intake of omega-3 fatty acids, determined by the DHA FFQ, showed no differences between groups at any time point (mean baseline DHA intake = 104 mg/d vs. mean week 24 intake = 112 mg/d). This dietary intake corresponds with the average American DHA intake: 110 mg/d for males; 80 mg/d for females, aged 60–69 years [37]. As expected, plasma phospholipid DHA levels significantly increased by 3.2 wt% in the DHA group by week 24. Changes in plasma phospholipid fatty acids are shown in Table 3 and correspond to the known alterations in fatty acids with DHA supplementation [29]. Week 24 log plasma DHA levels were significantly correlated with the change from baseline PAL response ($r = -.11$, $P = .024$) (Fig. 2). Compliance, measured by plasma DHA levels, was >82% in the DHA group and >99% in the placebo group. As a secondary measure, capsule counts demonstrated >91% compliance.

There were no significant differences between groups on hematology and clinical chemistry measures, including hemoglobin/hematocrit, white blood cell count, total cholesterol, glucose, hs-crp, and liver transaminases. Alkaline phosphatase showed a nonclinically significant mean decrease of 3.6 IU from baseline with DHA versus placebo ($P < .001$), although both groups were in the normal range, 73 and 75 IU, respectively at week 24. There were no significant differences in systolic or diastolic blood pressure with DHA administration; however, a significant decrease in heart rate was detected in the DHA group at week 24 compared to baseline (−3.2 ± .59 bpm vs. −1 ± 0.61 bpm placebo, $P < .03$). The prevalence of cardiovascular disease in the study sample was 68%, consistent with the general population of this age group, although a slightly lower incidence of hypertension (43%) was found in our sample compared with 65–74-year-old individuals (67%) who were included in National Health and Nutrition Examination survey (NHANES) [38]. As reported in Table 1, 36% of the sample were taking statins, 50% were taking anti-hypertensive medications, and 41% took multivitamins or aspirin (37%). Except for statin use, tests for drug interactions of concomitant medications with DHA were not conducted.

The number of treatment-emergent adverse events were reported and the number of subjects reporting those events was similar across groups (45% DHA; 44.9% placebo). Twenty-one serious adverse events (SAEs) in 14 subjects (3%) were reported (13 SAEs/7 DHA subjects; 8 SAEs/7 placebo subjects). No SAEs were considered by investigators as treatment-related events. No significant difference in the incidence of treatment-emergent adverse events or SAEs was observed between groups (Tables 4 and 5).

Table 2
Cognitive and functional tests

Cognitive or functional measure	Baseline score, mean (SD)	Week 24 score, mean (SD)	Week 24 change from baseline, mean (SE)	Between group difference score (SE)*	*P* value†
CANTAB PAL (6 pattern stage errors)					
900 mg DHA (n = 241)	13.4 (11.6)	8.8 (9.9)	−4.5 (0.64)	−1.63 (0.76)	.032‡
Placebo (n = 242)	12.1 (10.9)	9.7 (10.4)	−2.4 (0.62)		
VRM free recall, total correct					
900 mg DHA	5.7 (1.9)	5.8 (2.1)	0.1 (0.13)	0.1 (0.23)	.791
Placebo	5.8 (1.9)	5.8 (2.1)	0 (0.13)		
VRM, immediate, total correct					
900 mg DHA	10.8 (1.5)	11.0 (1.4)	0.2 (0.11)	0.4 (0.17)	.018‡
Placebo	10.9 (1.5)	10.9 (1.4)	0.0 (0.11)		
VRM, delayed, total correct					
900 mg DHA	10.4 (1.8)	10.7 (1.5)	0.3 (0.11)	0.5 (0.18)	.012‡
Placebo	10.5 (1.8)	10.7 (1.8)	0.1 (0.11)		
PRM, delayed, number correct					
900 mg DHA	9.5 (1.6)	8.6 (2.0)	−0.9 (0.13)	−0.1 (0.16)	.573
Placebo	9.7 (1.5)	8.8 (1.8)	−0.9 (0.12)		
SOC, problems solved					
900 mg DHA	3.5 (1.2)	3.5 (1.3)	0.1 (0.09)	−0.23 (0.11)	.045‡
Placebo	3.5 (1.4)	3.7 (1.3)	0.2 (0.10)		
SWM, between errors					
900 mg DHA	20.3 (9.1)	20.5 (9.3)	0.2 (0.54)	1.8 (0.99)	.066
Placebo	20.3 (10.8)	19.3 (10.4)	−0.9 (0.61)		
MMSE					
900 mg DHA	28.3 (1.3)	28.0 (1.9)	−0.4 (0.12)	0 (0.15)	.866
Placebo	28.2 (1.3)	27.9 (1.9)	−0.3 (0.11)		
Geriatric depression					
900 mg DHA	1.3 (1.2)	1.4 (1.6)	0.1 (0.10)	0.1 (0.12)	.230
Placebo	1.3 (1.3)	1.3 (1.5)	0.0 (0.08)		

Abbreviations: PAL, Paired Associate Learning; VRM, Verbal Recognition Memory; PRM, Pattern Recognition Memory; SOC, Stockings of Cambridge; SWM, Spatial Working Memory; MMSE, Mini Mental State Examination.

*Model-adjusted difference score.

†For the ITT population, based on an ANCOVA model with effects treatment, pooled site, age group, education level, baseline parameter score, and treatment by pooled site interaction, if significant.

‡$P < .05$.

4. Discussion

This clinical study demonstrated that 900 mg/d of DHA supplementation improved episodic memory and learning in healthy, older adults with mild memory complaints. Over 24 weeks, compared with placebo, DHA supplementation produced a significant 2-fold reduction in the number of visuospatial learning and episodic memory errors on the CANTAB PAL 6 pattern test and significant increases in VRM. Cognitive changes were significantly correlated with week 24 log plasma DHA levels. The DHA effects are significant in that they represent an objective demonstration of improved memory in ARCD. Clinically, compared to age-associated normative CANTAB data as a point of reference, DHA supplementation yielded a 7-year improvement in PAL test performance versus a 3.6-year improvement with placebo. The placebo response was likely due to a small retest effect which is common with cognitive tests such as the PAL [39]. Mean PAL errors at baseline corresponded to a cognitive age of 72.6 years, and following 24 weeks of DHA supplementation, a cognitive age of 65.6 years. A 3.4 year *net* improvement in learning and memory function with DHA is likely beneficial to aging adults with mild memory complaints.

As described in reviews that consider various tools used for cognitive testing, the CANTAB PAL test appears to be a well-characterized episodic memory test that depends on mnemonic processes of the medial temporal lobe [22,40]. Studies have demonstrated that the PAL seems to discriminate well between healthy controls, mild cognitively impaired

Table 3
Plasma phospholipid fatty acids

Fatty acid	900 mg/d DHA (n = 209) change from baseline*	Placebo (n = 212) change from baseline*	*P* value†
DHA	3.2	−0.08	.001
ARA	−1.4	−0.12	.001
EPA	0.16	−0.06	.001
DPA n-6	0.38	−0.004	.001

Abbreviations: DHA, docosahexaenoic acid; ARA, arachidonic acid; EPA, eicosapentaenoic acid; DPAn-6, docosapentaenoic acid.

*Weight % of total fatty acids.

†Based on ANCOVA model with effects treatment, pooled site, age group, education level, baseline parameter, concomitant statin use (if significant), and treatment by pooled site interaction, if significant.

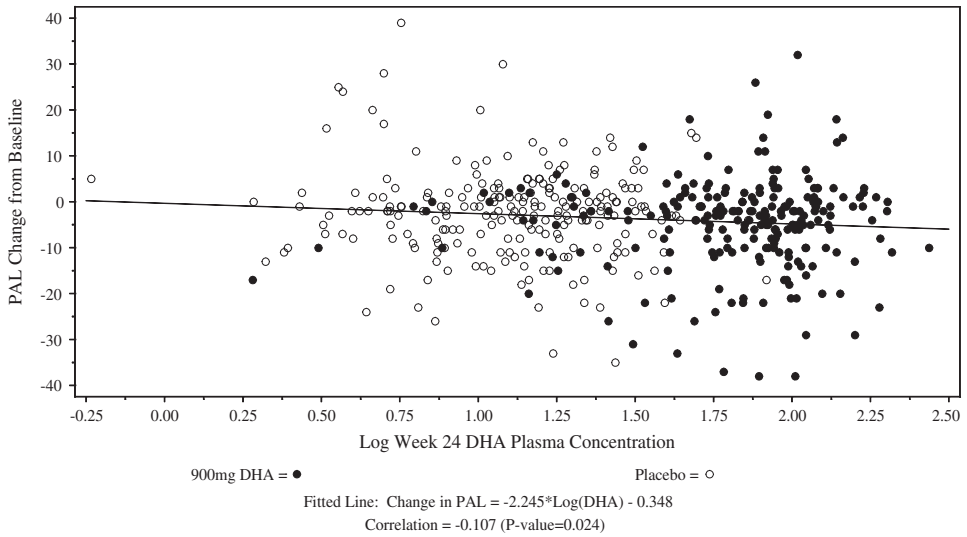

Fig. 2. Correlation of PAL change from baseline errors with plasma DHA levels. Scatterplot of the change from baseline in PAL errors (6 shapes) and the log week 24 DHA plasma levels (wt%) in ITT, LOCF population. Fitted linear regression line: change in PAL = −2.245*log (DHA)–0.348; $r = -.107$, $P = .024$. DHA = •, Placebo = O.

individuals, and AD patients [23,25,41]. The number of baseline PAL errors observed in our study are in line with previous trials that have also identified individuals with mild memory loss and illustrate mean scores that lie between those with normal cognition and MCI or ''questionable dementia'' [22]. The current results suggest that DHA supplementation may ameliorate early memory and learning deficits associated with cognitive aging [40].

The results also indicate that subjects in the DHA group who had lower baseline delayed recall Logical Memory scores showed greater improvement on the PAL. This finding supports the positive episodic memory effects resulting from DHA supplementation. A lower cut-off for the Logical Memory test was not established at entry. Thus, we cannot rule out the possibility that a few of these subjects with the lowest baseline scores would meet criteria for MCI. Within the DHA group, other cofactors, such as family history of dementia, and concomitant statin use were also associated with better performance on the PAL. This finding suggests that potential genetic and cardiovascular factors may influence the effects of DHA on cognition. Approximately 36% of the sample had a family history of dementia. APOE4 genotyping, as a risk factor for dementia, was not conducted and thus remains an interesting factor to further explore with DHA supplementation.

Cardiovascular disease, including hypertension, is considered by some to be a potential risk factor for cognitive disorders such as dementia [42]. Within our study population, 68% had a history of cardiovascular disease, 36% were taking statins, and 50% were on anti-hypertensives, suggesting comorbidity of cognitive and cardiovascular problems in aging individuals which may be ameliorated with additional DHA supplementation. It is noteworthy that there was a significant decrease in heart rate associated with DHA supplementation which may help reduce the risk of fatal cardiovascular events in this age group [43].

DHA supplementation did not produce changes in working memory (SWM) and executive function (SOC), cognitive

Table 4
Incidence of treatment-emergent adverse events

	DHA (n = 242)	Placebo (n = 243)	*P* value†
AEs by SOC*	n = 109	n = 109	
Number of subjects with AEs	n (%)	n (%)	
Infections/infestations	32 (13.2)	41 (16.9)	.310
Gastrointestinal disorders	30 (12.4)	41 (16.9)	.199
Musculoskeletal/connective tissue disorders	17 (7.0)	14 (5.8)	.584
Nervous system disorders	16 (6.6)	10 (4.1)	.234
Skin/subcutaneous tissue disorders	12 (5.0)	8 (3.3)	.373

*Adverse Events or Serious Adverse Events by MedDRA System Organ Class occurring in 5% or greater of subjects in either group.

†Fisher's Exact Test.

Table 5
Incidence of treatment-emergent serious adverse events

	DHA	Placebo
SAEs by SOC*	n = 7	n = 7
Number of subjects with SAEs†,‡	n	n
Infections/infestations	2	3
Musculoskeletal	2	0
Gastrointestinal	1	1
Nervous system	0	1

*Adverse Events or Serious Adverse Events by MedDRA System Organ Class occurring in 5% or greater of subjects in either group.

†Some subjects had multiple SAEs.

‡Two deaths unrelated to product: (1) congestive heart failure; (1) chronic obstructive pulmonary disease.

functions that are typically impaired in multidomain MCI and later stages of AD. Similar findings were also shown in a study of ''robust'' versus ''non-robust memory'' participants [22]. It is possible that significant changes in these other cognitive domains would be seen with more severe cognitive impairment or longer DHA supplementation, but this awaits confirmation. The MMSE and Geriatric Depression scale were unchanged in both groups over the 24-week period. Self-assessment tests of memory and daily living skills showed trends of improvement over time but no differential effects with DHA. This is likely due to the mild cognitive deficits of the study sample that typically show no functional activity impairment. The 900 mg/d dose of DHA doubled plasma DHA levels as expected and was well tolerated with good compliance.

DHA plays an essential role in neuronal development and in multiple brain functions. Previous clinical studies with LCPUFAs have demonstrated small but significant benefits in patients with MCI or mild AD. However, no benefits were demonstrated in a recent study of cognitively healthy elders [17]. In this study, the mean MMSE score was 28, yet the range of impairment was wide (MMSE scores, 23–30) which likely contributed to greater variability in cognitive responses among treatment groups. Recruited subjects had an average LCPUFA intake of ~300 mg/d, higher than the average U.S. intake (~100 mg/d) [37]. Thus, higher baseline intake status may have reduced the ability to identify cognitive improvements. This study also found significant ceiling effects with the cognitive tests administered, making it difficult to detect an omega-3 benefit. Differences in study design may have accounted for our dissimilar positive results.

Our results are the first to clinically confirm that DHA significantly improves episodic memory and learning functions in healthy adults with ARCD. The magnitude of the improvement in episodic memory may appear to be moderate. However, considering the duration of treatment (24 weeks) and the fact that healthy older adults with mild memory loss were considered the findings reported herein are important. Some studies have also shown that changes in episodic memory can be determined by the PAL test, and such changes are predictive of pre-clinical AD [39,40]. The positive findings here indicate that 900 mg/d of DHA may serve as a nutritional neuroprotective agent in improving some very early cognitive deficits. Such cognitive changes likely occur as a consequence of normal aging or may be observed before a diagnosis of MCI or mild AD. The present study was not designed to assess long-term effects of DHA on cognitive decline rates or conversion rates to MCI or mild AD. On the basis of epidemiological and clinical data to date, DHA is potentially beneficial for prevention of cognitive decline but will need confirmation with long-term prevention trials (*www.clinicaltrials.gov*). Our study results demonstrate that DHA is well tolerated and may have a significant positive effect on gradual memory loss, which is a major health concern of older individuals.

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UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Edith Ramirez, Chairwoman**
Julie Brill
Maureen K. Ohlhausen
Joshua D. Wright
Terrell McSweeny

In the Matter of	)	
	)	**DOCKET NO. C-4486**
I-HEALTH, INC.,	)	
a corporation, and	)	
	)	
MARTEK BIOSCIENCES CORP.,	)	
a corporation.	)	
	)	

DECISION AND ORDER

The Federal Trade Commission ("Commission") having initiated an investigation of certain acts and practices of the respondents named in the caption hereof, and the respondents having been furnished thereafter with a copy of a draft complaint that the Bureau of Consumer Protection proposed to present to the Commission for its consideration and which, if issued by the Commission, would charge the respondents with violation of the Federal Trade Commission Act, 15 U.S.C. § 45 *et seq.*; and

The respondents, their attorneys, and counsel for the Commission having thereafter executed an agreement containing a consent order ("consent agreement") that includes: a statement that the agreement is for settlement purposes only and does not constitute an admission that the law has been violated as alleged in the draft complaint, or that the facts as alleged in the draft complaint, other than the jurisdictional facts, are true; and waivers and other provisions as required by the Commission's Rules; and

The Commission having thereafter considered the matter and having determined that it has reason to believe that the respondents have violated the Federal Trade Commission Act, and that a complaint should issue stating its charges in that respect, and having thereupon accepted the executed consent agreement and placed such consent agreement on the public record for a period of thirty (30) days for the receipt and consideration of public comment, and having duly considered the comments filed thereafter by interested persons pursuant to Commission Rule 2.34, 16 C.F.R. § 2.34, now in further conformity with the procedure prescribed in Commission

Rule 2.34, the Commission hereby issues its complaint, makes the following jurisdictional findings, and enters the following order:

1. Respondent i-Health, Inc. is a Delaware corporation with its principal office or place of business at 55 Sebethe Drive, Cromwell, Connecticut 06416.

2. Respondent Martek Biosciences Corporation was a Delaware corporation with its principal office or place of business at 6480 Dobbin Road, Columbia, Maryland 21045. On June 30, 2012, Martek Biosciences Corporation merged into its successor, DSM Nutritional Products, LLC. DSM Nutritional Products, LLC is a Delaware corporation with its principal office or place of business at 45 Waterview Boulevard, Parsippany, New Jersey 07054.

3. The Commission has jurisdiction of the subject matter of this proceeding and of the respondents, and the proceeding is in the public interest.

ORDER

DEFINITIONS

For purposes of this order, the following definitions shall apply:

1. Unless otherwise specified, "Respondents" means i-Health, Inc. and Martek Biosciences Corporation, and their successors and assigns.

2. DSM Nutritional Products, LLC is a successor of Martek Biosciences Corporation.

3. "Commerce" means as defined in Section 4 of the Federal Trade Commission Act, 15 U.S.C. § 44.

4. "Covered Product" means any dietary supplement, food, or drug promoted to prevent cognitive decline or improve memory, or containing docosahexaenoic acid ("DHA"), including, but not limited to, BrainStrong Adult. Covered Product does not include infant formula or ingredients when sold specifically for use in infant formula.

5. "Dietary supplement" means:

   A. any product labeled as a dietary supplement or otherwise represented as a dietary supplement; or

   B. any pill, tablet, capsule, powder, softgel, gelcap, liquid, or other similar form containing one or more ingredients that are a vitamin, mineral, herb or other botanical, amino acid, probiotic, or other dietary substance for use by humans to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above,

that is intended to be ingested, and is not represented to be used as a conventional food or as a sole item of a meal or the diet.

6. "Endorsement" means as defined in 16 C.F.R. § 255.0.

7. "Food" and "drug" mean as defined in Section 15 of the FTC Act, 15 U.S.C. § 55.

8. The term "including" in this order means "without limitation."

9. The terms "and" and "or" in this order shall be construed conjunctively or disjunctively as necessary, to make the applicable phrase or sentence inclusive rather than exclusive.

10. "Reliably Reported," for a human clinical test or study ("test"), means a report of the test has been published in a peer-reviewed journal, and such published report provides sufficient information about the test for experts in the relevant field to assess the reliability of the results.

I.
Prohibited Memory and Cognitive Decline Claims

IT IS ORDERED that Respondents and their officers, agents, representatives, and employees, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, shall not make any representation, in any manner, expressly or by implication, including through the use of a product name, endorsement, depiction, illustration, trademark, or trade name, that such product:

A. improves memory in adults; or

B. prevents cognitive decline in adults,

unless the representation is non-misleading and, at the time of making such representation, Respondents possess and rely upon competent and reliable scientific evidence to substantiate that the representation is true. For purposes of this Section, competent and reliable scientific evidence shall consist of human clinical testing that is sufficient in quality and quantity, based on standards generally accepted by experts in cognitive science, when considered in light of the entire body of relevant and reliable scientific evidence, to substantiate that the representation is true. Such testing shall be randomized, double-blind, and placebo-controlled; and be conducted by researchers qualified by training and experience to conduct such testing. In addition, all underlying or supporting data and documents generally accepted by experts in cognitive science as relevant to an assessment of such testing, as set forth and described in the Part of this Order entitled Preservation of Records Relating to Competent and Reliable Human Clinical Tests or Studies, must be available for inspection and production to the Commission.

II.
Prohibited Health Benefit Claims

IT IS FURTHER ORDERED that Respondents and their officers, agents, representatives, and employees, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, shall not make any representation, in any manner, expressly or by implication, including through the use of a product name, endorsement, depiction, illustration, trademark, or trade name, other than representations covered under Part I of this order, about the health benefits, performance, safety, or efficacy of any Covered Product, unless the representation is non-misleading, and, at the time of making such representation, the Respondents possess and rely upon competent and reliable scientific evidence that is sufficient in quality and quantity based on standards generally accepted in the relevant scientific fields, when considered in light of the entire body of relevant and reliable scientific evidence, to substantiate that the representation is true. For purposes of this Part, competent and reliable scientific evidence means tests, analyses, research, or studies that (1) have been conducted and evaluated in an objective manner by qualified persons; (2) are generally accepted in the profession to yield accurate and reliable results; and (3) as to which, when they are human clinical tests or studies, all underlying or supporting data and documents generally accepted by experts in the field as relevant to an assessment of such testing, as set forth in the Part of this Order entitled Preservation of Records Relating to Competent and Reliable Human Clinical Tests or Studies, are available for inspection and production to the Commission.

III.
Prohibited Representations Regarding Tests or Studies

IT IS FURTHER ORDERED that Respondents and their officers, agents, representatives, and employees, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, shall not misrepresent, in any manner, expressly or by implication, including through the use of a product name, word, phrase such as “clinically shown” or “clinically proven,” endorsement, depiction, illustration, trademark, or trade name:

A. The existence, contents, validity, results, conclusions, or interpretations of any test, study, or research; or

B. That any benefits of such Covered Product are scientifically or clinically proven, including, but not limited to, that the Covered Product is clinically proven to improve memory in adults.

IV.
FDA Approved Claims

IT IS FURTHER ORDERED that nothing in this order shall prohibit Respondents from making any representation for:

A. Any drug that is permitted in labeling for such drug under any tentative or final standard promulgated by the Food and Drug Administration, or under any new drug application approved by the Food and Drug Administration; or

B. Any product that is specifically permitted in labeling for such product by regulations promulgated by the Food and Drug Administration pursuant to the Nutrition Labeling and Education Act of 1990 or permitted under Sections 303-304 of the Food and Drug Administration Modernization Act of 1997.

V.
Record Keeping Requirements

IT IS FURTHER ORDERED that Respondents shall, for five (5) years after the last date of dissemination of any representation covered by this order, maintain and upon request make available to the Commission for inspection and copying:

A. All advertisements, labeling, packaging, and promotional materials containing the representation;

B. All materials that were relied upon in disseminating the representation; and

C. All tests, reports, studies, surveys, demonstrations, or other evidence in their possession or control that contradict, qualify, or call into question the representation, or the basis relied upon for the representation, including complaints and other communications with consumers or with governmental or consumer protection organizations.

VI.
Preservation of Records Relating to Competent and Reliable Human Clinical Tests or Studies

IT IS FURTHER ORDERED that, with regard to any human clinical test or study ("test") upon which Respondents rely to substantiate any claim covered by this Order, Respondents shall secure and preserve all underlying or supporting data and documents generally accepted by experts in the field as relevant to an assessment of the test, including, but not necessarily limited to:

A. All protocols and protocol amendments, reports, articles, write-ups, or other accounts of the results of the test, and drafts of such documents reviewed by the test sponsor or any other person not employed by the research entity;

B. All documents referring or relating to recruitment; randomization; instructions, including oral instructions, to participants; and participant compliance;

C. Documents sufficient to identify all test participants, including any participants who did not complete the test, and all communications with any participants relating to the test, all raw data collected from participants enrolled in the test, including any participants who did not complete the test; source documents for such data; any data dictionaries; and any case report forms;

D. All documents referring or relating to any statistical analysis of any test data, including, but not limited to, any pretest analysis, intent-to-treat analysis, or between-group analysis performed on any test data; and

E. All documents referring or relating to the sponsorship of the test, including all communications, including contracts, between any sponsor and the test's researchers.

Provided, however, the preceding preservation requirement shall not apply to a Reliably Reported test, unless the test was conducted, controlled, or sponsored, in whole or in part (1) by any Respondent, or by any person or entity affiliated with or acting on behalf of any Respondent, including officers, agents, representatives, and employees, or by any other person or entity in active concert or participation with any Respondent ("Respondent's affiliates"), (2) by the supplier or manufacturer of the product at issue, or (3) by a supplier to any Respondent, to Respondent's affiliates, or to the product's manufacturer of any ingredient contained in such product.

For any test conducted, controlled, or sponsored, in whole or in part, by Respondents, Respondents must establish and maintain reasonable procedures to protect the confidentiality, security, and integrity of any personal information collected from or about participants. These procedures shall be documented in writing and shall contain administrative, technical, and physical safeguards appropriate to Respondents' size and complexity, the nature and scope of Respondents' activities, and the sensitivity of the personal information collected from or about the participants.

VII.
Order Acknowledgements

IT IS FURTHER ORDERED that Respondents shall deliver a copy of this order to all current and future principals, officers, and directors, and to all current and future employees, agents, and representatives having managerial responsibilities with respect to the subject matter of this order. Respondents shall secure from each such person a signed and dated statement acknowledging receipt of the order. Respondents shall deliver this order to such current

personnel within thirty (30) days after the date of service of this order, and to future personnel within thirty (30) days after the person assumes such position or responsibilities.

VIII.
Compliance Notification

IT IS FURTHER ORDERED that Respondents shall notify the Commission at least thirty (30) days prior to any change in the corporations that may affect compliance obligations arising under this order, including, but not limited to, a dissolution, assignment, sale, merger, or other action that would result in the emergence of a successor entity; the creation or dissolution of a subsidiary, parent, or affiliate that engages in any acts or practices subject to this order; the proposed filing of a bankruptcy petition; or a change in the business or corporate name or address. Provided, however, that, with respect to any proposed change in the corporation(s) about which Respondents learn less than thirty (30) days prior to the date such action is to take place, Respondents shall notify the Commission as soon as is practicable after obtaining such knowledge. Unless otherwise directed by a representative of the Commission, all notices required by this Part shall be sent by overnight courier (not the U.S. Postal Service) to the Associate Director for Enforcement, Bureau of Consumer Protection, Federal Trade Commission, 600 Pennsylvania Avenue NW, Washington, DC 20580, with the subject line i-Health, Inc., FTC File No. 122-3067. *Provided, however*, that, in lieu of overnight courier, notices may be sent by first class mail, but only if electronic versions of such notices are contemporaneously sent to the Commission at DEbrief@ftc.gov.

IX.
Compliance Reporting

IT IS FURTHER ORDERED that Respondents, within one hundred twenty (120) days after the date of service of this order, shall file with the Commission a true and accurate report, in writing, setting forth in detail the manner and form of their compliance with this order. Within ten (10) days of receipt of written notice from a representative of the Commission, they shall submit additional true and accurate written reports.

X.
Order Termination

This order will terminate on August 21, 2034, or twenty (20) years from the most recent date that the United States or the Commission files a complaint (with or without an accompanying consent decree) in federal court alleging any violation of the order, whichever comes later; provided, however, that the filing of such a complaint will not affect the duration of:

A. Any part in this order that terminates in less than twenty (20) years;

B. This order's application to any Respondent that is not named as a Respondent in such complaint; and

C. This order if such complaint is filed after the order has terminated pursuant to this Part.

Provided, further, that if such complaint is dismissed or a federal court rules that Respondents did not violate any provision of the order, and the dismissal or ruling is either not appealed or upheld on appeal, then the order will terminate according to this Part as though the complaint had never been filed, except that the order will not terminate between the date such complaint is filed and the later of the deadline for appealing such dismissal or ruling and the date such dismissal or ruling is upheld on appeal.

By the Commission, Commissioner Ohlhausen dissenting and Commissioner McSweeny not participating.

Donald S. Clark
Secretary

SEAL:
ISSUED: August 21, 2014

Statement of Chairwoman Edith Ramirez and Commissioner Julie Brill
In the Matter of i-Health, Inc. and Martek Biosciences Corporation
June 6, 2014

We write to explain our support for the complaint and order imposed against respondents i-Health, Inc. and Martek Biosciences Corporation (collectively, "i-Health") with respect to advertising claims that their BrainStrong Adult dietary supplement improves adult memory and is clinically proven to do so. Section 5 of the FTC Act requires that advertisers have a reasonable basis for the claims they make to ensure that their claims are truthful and non-deceptive.[1] We have reason to believe that i-Health fell short of this standard.

i-Health advertises a dietary supplement, BrainStrong Adult, containing docosahexaenoic acid ("DHA"), with broad and prominent claims that the product is "[c]linically shown to improve memory." Its advertising also makes the general efficacy claim that BrainStrong improves memory. Consumers would likely have reasonably interpreted these claims broadly to include a wide variety of promises of real-life improvements in memory, such as the ability to remember the location of one's sunglasses or why one entered a room – which is the precise scenario depicted in i-Health's television ad.[2] We do not believe that i-Health possessed the evidence necessary to back up such reasonable interpretations by consumers. Accordingly, we allege that i-Health's efficacy claim was unsubstantiated and that its establishment claim was false and misleading.[3]

i-Health's establishment claim that BrainStrong Adult is clinically proven to improve adult memory requires, by its own terms, a well-controlled human clinical study.[4] Its efficacy claim about its dietary supplement must be supported by competent and reliable scientific evidence.[5] In support of these claims, i-Health relies primarily on a double-blind, placebo-

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[1] *FTC Policy Statement Regarding Advertising Substantiation*, 104 F.T.C. 839 (1984) (appended to *Thompson Med. Co.*, 104 F.T.C. 648 (1984)) ("*Substantiation Statement*") ("[W]e reaffirm our commitment to the underlying legal requirement of advertising substantiation – that advertisers and ad agencies have a reasonable basis for advertising claims before they are disseminated."), *aff'd*, 791 F.2d 189, 193 & 196 (D.C. Cir. 1986), *cert. denied*, 479 U.S. 1086 (1987).

[2] *See* FTC, *Dietary Supplements: An Advertising Guide for Industry* 3-4 (Apr. 2001) ("*Dietary Supplements Guide*"), *available at* http://business.ftc.gov/documents/bus09-dietary-supplements-advertising-guide-industry ("When an ad lends itself to more than one reasonable interpretation, the advertiser is responsible for substantiating each interpretation."); *see also id.* at 12.

[3] The Commission also alleges that i-Health made the unsubstantiated claim that BrainStrong prevents cognitive decline in adults. Because the Commission has unanimously voted in favor of this allegation, we do not address it here.

[4] *Substantiation Statement* at 839 ("When the substantiation claim is express (e.g., 'tests prove,' 'doctors recommend,' and 'studies show'), the Commission expects the firm to have at least the advertised level of substantiation."); *Removatron Int'l Corp.*, 111 F.T.C. 206, 297-99 (1988) ("If an advertisement represents that a particular claim has been scientifically established, the advertiser must possess a level of proof sufficient to satisfy the relevant scientific community of the claim's truth."), *aff'd*, 884 F.2d 1489 (1st Cir. 1989).

[5] *Dietary Supplements Guide* at 9.

controlled clinical study published in a peer-reviewed journal – the Memory Improvement with Docosahexaenoic Acid Study ("MIDAS study"). The study purports to show that DHA "improves episodic memory" and "memory function." The MIDAS study's principal investigator and author was an employee of respondent Martek.[6]

As an initial matter, regardless of the methodology and purported findings of the MIDAS study, the first question we ask is what the study was designed to measure and demonstrate. Stated differently, and more directly for our purposes, does the study, assuming it was well-conducted, substantiate i-Health's broad claims that BrainStrong improves memory and that it was "clinically shown" to do so? Contrary to the view of Commissioner Ohlhausen, we do not think it does.

As detailed in the complaint, there are several types of human memory, including episodic memory, sensory memory, working memory, semantic memory, and procedural memory. Importantly, the MIDAS study tested tasks associated with only two types of memory: episodic memory, the recollection of specific personal events linked to a time and place, such as where someone left her car keys; and working memory, the short-term mental manipulation of information, such as the ability to follow a story or discussion. Notably, the study reports only a very small improvement from BrainStrong in relation to episodic memory – the positive result was essentially limited to performance on a single test of one of three types of episodic memory that were measured (visuospatial). The study did not reveal any improvement in working memory. In light of the narrow scope of the study and its limited results, we have reason to believe that i-Health's marketing claims that BrainStrong improves "memory" broadly speaking would likely mislead consumers, as there is no basis to conclude that it has any impact whatsoever on other important facets of memory, such as the ability to remember the meaning of words (semantic memory) or to follow an exchange of dialogue (working memory). This alone would be reason enough for us to conclude that the MIDAS study does not adequately substantiate i-Health's general memory improvement claims.

But our concerns extend even further. As we have also alleged in the complaint, the MIDAS study did not show a pattern of statistically and clinically significant improvements on the episodic memory tasks among subjects who took BrainStrong's DHA, relative to the placebo group. Specifically, it failed to show meaningful, statistically significant improvements on two of the three episodic memory tasks measured. Further, it failed to demonstrate that the very small, statistically significant improvement on one of those tasks that it did report correlates with improvements in memory tasks outside of the laboratory.[7] We believe that reasonable consumers would likely be misled that BrainStrong will result in the kinds of real-life improvements depicted in i-Health's advertising.

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[6] Karin Yurko-Mauro et al., *Beneficial Effects of Docosahexaenoic Acid on Cognition in Age-Related Cognitive Decline*, 6 Alzheimer's & Dementia 456 (2010).

[7] *See Dietary Supplements Guide* at 12 ("Some results that are statistically significant may still be so small that they would mean only a trivial effect on consumer health.").

It is correct, as Commissioner Ohlhausen notes in her dissent, that some of the statements made by the study's authors in the "Results" and "Discussion" sections of the MIDAS study use language similar to that in i-Health's memory improvement claims. However, we disagree that the Commission must accept at face value these statements as supportive of the claims in i-Health's advertising. Doing so would be inconsistent with the Commission's obligation to assess the quality and reliability of the scientific evidence underlying challenged advertising claims.[8] Our conclusions are based on extensive consultations with experts in the cognitive science and biostatistics fields. Consistent with the requirements of Section 5 and our past practice,[9] we undertook an evaluation of the results of the MIDAS study to assess whether they substantiated i-Health's advertising claims and did not simply defer to the authors' interpretations of their results.[10]

For all of the foregoing reasons, we have reason to believe that i-Health lacked adequate substantiation for the broad marketing claims that BrainStrong Adult improves adult memory, that i-Health's clinical-proof claims are false and misleading, and that the relief set forth in the proposed order is appropriate.

[8] Commissioner Ohlhausen also observes that the complaint does not take issue with how i-Health conducted the clinical testing component of the trial, *i.e.*, that it was a large, multi-center trial that was randomized, placebo-controlled, and double-blinded. However, sometimes such studies ultimately yield inconclusive or weak findings, as was the case with the MIDAS study.

[9] *See, e.g., Schering Corp.*, 118 F.T.C. 1030, 1084, 1095 (1994). *See also Unither Pharma, Inc.*, 136 F.T.C. 145, 161 (2003).

[10] In addition to the MIDAS study, our experts in the cognitive science and biostatistics fields also reviewed the totality of other evidence that i-Health proffered on DHA and memory, finding those results to be inadequate to back i-Health's claims as well.

Separate Statement of Commissioner Maureen K. Ohlhausen
Dissenting in Part
In the Matter of i-Health, Inc. and Martek Biosciences Corporation
June 5, 2014

The Commission has long interpreted Section 5 of the FTC Act[1] to require an advertiser to have a reasonable basis for making an objective claim about its product.[2] As we execute this mandate, we must be mindful of what we are trying to accomplish, however. As former FTC Chairman Robert Pitofsky stated, the overall goal of evaluating advertising claims is not "a broad, theoretical effort to achieve Truth, but rather a practical enterprise to ensure the existence of reliable data which in turn will facilitate an efficient and reliable competitive market process."[3]

I dissent in part from today's action because it imposes an unduly high standard of substantiation on a safe product. This unduly high standard not only risks denying consumers useful information in the present but may also, in the long term, diminish incentives to conduct research on the health effects of foods and dietary supplements and reduce the incentives of manufacturers to introduce such products.[4] The majority's approach may ultimately undermine an efficient and reliable competitive market process and make consumers worse off.[5]

The complaint in this matter challenges the efficacy claim that BrainStrong Adult (a DHA supplement) improves memory in adults and the establishment claim that BrainStrong Adult is clinically proven to improve memory in adults.[6] Advertisers must support claims of efficacy of dietary supplements with "competent and reliable scientific evidence."[7] For establishment

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[1] 15 U.S.C. § 45(a).

[2] FTC Policy Statement Regarding Advertising Substantiation (appended to *Thompson Med. Co., Inc.*, 104 F.T.C. 648, 840 (1984)).

[3] Robert Pitofsky, *Beyond Nader: Consumer Protection and the Regulation of Advertising*, 90 HARV. L. REV. 661, 671 (1977).

[4] *See* Statement of Commissioner Maureen K. Ohlhausen, Dissenting in Part and Concurring in Part, *In the Matter of GeneLink, Inc., et al.*, FTC Docket No. C4456, at 2 (Jan. 7, 2014) ("Although raising the requirement for both the number and the rigor of studies required for substantiation for all health- or disease-related claims may increase confidence in those claims, the correspondingly increased burdens in time and money in conducting such studies may suppress information that would, on balance, benefit consumers.").

[5] *See id.* ("If we demand too high a level of substantiation in pursuit of certainty, we risk losing the benefits to consumers of having access to information about emerging areas of science and the corresponding pressure on firms to compete on the health features of their products."); FTC Staff Comment Before the Food and Drug Administration In the Matter of Assessing Consumer Perceptions of Health Claims, Docket No. 2005N-0413, at 5-6 (2006) (noting the FTC's advertising enforcement seeks to avoid "unduly burdensome restrictions that might chill information useful to consumers in making purchasing decisions.") *available at* http://www.ftc.gov/be/V060005.pdf.

[6] The complaint also challenges the efficacy claim that BrainStrong Adult prevents cognitive decline. I agree with the majority that the proffered study does not support this claim.

[7] The FTC's *Dietary Supplements: An Advertising Guide for Industry* defines competent and reliable scientific evidence as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." It further states that well-controlled human clinical trials are the "most reliable form of evidence." *See Dietary Supplements: An Advertising*

claims, where advertisements refer to a certain level of support, advertisers "must be able to demonstrate that the assertion is accurate [and] have the level of support that they claim, expressly or by implication, to have."[8]

In this matter, the defendant offers as the primary substantiation for its claims the MIDAS study, a placebo-controlled, randomized, double-blind, parallel, multi-center, six-month, peer-reviewed, journal-published study of 485 subjects with statistically significant results.[9] Specifically, the MIDAS study concluded:

- "This clinical study demonstrated that 900 mg/d of DHA supplementation improved episodic memory and learning in healthy, older adults with mild memory complaints.... The DHA effects are significant in that they represent an objective demonstration of improved memory in [age-related cognitive decline]."[10]
- "Our results are the first to clinically confirm that DHA significantly improves episodic memory and learning functions in healthy adults with [age-related cognitive decline]."[11]
- "Our study results demonstrate that DHA is well tolerated and may have significant positive effect on gradual memory loss...."[12]

These conclusions match up well with the "improves memory" efficacy claim and the "clinically proven to improve memory" establishment claim.[13] Thus, I believe this study, in the context of other supporting studies involving DHA and memory,[14] provides a reasonable basis for the "improves memory" claims.[15]

Guide for Industry at 9 ("*Dietary Supplements Guide*"), *available at* http://business.ftc.gov/sites/default/files/pdf/bus09-dietary-supplements-advertising-guide-industry.pdf.

[8] *Id.*

[9] *See* Karin Yurko-Mauro *et al.*, *Beneficial Effects of Docosahexaenoic Acid on Cognition in Age-Related Cognitive Decline*, 6 ALZHEIMER'S & DEMENTIA 456 (2010) ("MIDAS study").

[10] *Id.* at 461.

[11] *Id.* at 463.

[12] *Id.*

[13] BrainHealth Adult product packaging also included language stating, "A recent clinical study showed that adults over 55 with a mild memory complaint who took 900mg/day of life'sDHA for 6 months improved their short-term memory."

[14] Martek cited many studies, including: a wide body of animal and cell culture studies that are consistent with the importance of DHA in cognitive function and suggest a potential mechanism for DHA's ability to support memory; numerous epidemiological studies identifying a correlation between DHA consumption and cognitive function; multiple clinical trials with generally supportive (although not wholly consistent) results; and seven reviews by independent expert bodies confirming the importance of DHA in supporting cognitive function. Not all of these studies are squarely on point, and some of them contain methodological weaknesses or inconclusive results. As such, their probity varies, but taken together they are supportive of DHA's positive role in brain function. The FTC must evaluate the well-conducted, statistically significant MIDAS study within the totality of this supportive evidence. *See Dietary Supplements Guide* at 14 ("Studies cannot be evaluated in isolation. The surrounding context of scientific evidence is just as important as the internal validity of individual studies.").

[15] Because the claims at issue here closely parallel the conclusions of the MIDAS study, this case differs from others where companies possessed well-conducted clinical trials yielding statistically significant results but made claims beyond the trials' ability to support. *Cf. Nestle HealthCare Nutrition, Inc.*, 151 F.T.C. 1 (2011) (defendant claimed

The complaint offers two reasons why the MIDAS study, despite being well-conducted and having statistically significant results, does not substantiate Martek's claims for BrainStrong Adult. First, the complaint argues that the "improves memory" claim is unsubstantiated because the MIDAS study did not show that BrainStrong Adult improved performance for all types of memory. However, the MIDAS study did demonstrate a statistically significant improvement in performance on episodic memory tasks. An improvement in episodic memory is indeed an improvement in memory, and the claim accurately conveys the study's findings in consumer vernacular.

Second, instead of criticizing the study's methodology, the complaint criticizes its conclusions. The complaint asserts that the MIDAS study "did not yield a pattern of statistically and clinically significant improvement" in memory.[16] This conclusion is based on the opinion of experts retained by FTC staff. The eight MIDAS study co-authors clearly disagree with this conclusion, as demonstrated by their own conclusions in the study.

The fact that some experts may disagree with the conclusions of a well-conducted study does not render that study unreliable or incompetent, nor make claims based on the study unsubstantiated. Specifically, Martek's reliance upon the MIDAS study, which was both well-conducted and consistent with other research, is not rendered unreasonable by the existence of some disagreement among experts. Indeed, "some disagreement" is the usual state of science.[17]

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its product reduced the duration of acute diarrhea in children up to the age of thirteen; studies only applied to infants and could not be extrapolated to older children); *Kellogg Co.*, FTC Docket No. C-4262 (2009) (defendant claimed that children who ate Frosted MiniWheats for breakfast were "nearly 20%" or "up to 18%" more attentive three hours later than children who ate nothing; study calculated average increased attention as ~10% and over half of children showed no benefit from eating the cereal).

[16] It is undisputed that the MIDAS study's primary endpoint (the CANTAB Paired Associate Learning, or "PAL," test) yielded statistically significant results, with a p-value of 0.032. As the Commission has stated, "significance with a p-value that is less than or equal to 0.05 is the recognized standard to show that a study's hypothesis has been proven." *POM Wonderful LLC*, Opinion of the Commission, 2013 FTC Lexis 6 at *77 (2013). Furthermore, the MIDAS study demonstrated that the difference in PAL scores between the test group and the placebo group was equivalent to a net 3.4-year improvement in performance, offering evidence of a clinically significant result.

[17] "The game of science is, in principle, without end. He who decides one day that scientific statements do not call for any further test, and that they can be regarded as finally verified, retires from the game." Karl Popper, THE LOGIC OF SCIENTIFIC DISCOVERY 32 (Taylor & Francis Group, 2005).

U.S. Department of Health & Human Services National Institutes of Health

NIH Office of Dietary Supplements

Omega-3 Fatty Acids and Health

Fact Sheet for Health Professionals

About the reports

This document summarizes the results of eight evidence-based reviews on the effects of omega-3 fatty acids from food or dietary-supplement sources for the prevention and treatment of several diseases. These reviews were prepared under contract to the Agency for Healthcare Research and Quality (AHRQ). All reviews were sponsored and funded by the Office of Dietary Supplements (ODS) of the National Institutes of Health, U.S. Department of Health and Human Services. Five reports were published in March 2004 and 3 additional reports were published in February 2005, all of which are available in their entirety and summary form on the ODS web site (ods.od.nih.gov) and the AHRQ web site (www.ahrq.gov).

Table of Contents

Three reports focus on cardiovascular disease (CVD), including the effects of omega-3 fatty acids on cardiac electrophysiology and arrhythmia (the heart's beating rate and disorders of its rhythm), cardiovascular risk factors such as blood pressure, and intermediate markers of disease such as heart rate variability [1-3]. One report focuses on omega-3 fatty acids and asthma. Another report addresses the effects of omega-3 fatty acids on type II diabetes and the metabolic syndrome, inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis [5]. Another report addresses the effects of omega-3 fatty acids on cognitive function in normal aging, the incidence and treatment of dementia, the incidence of Parkinson's disease and cerebral palsy in infants, and clinical outcomes in progressive multiple sclerosis [6]. Another report evaluates whether omega-3 fatty acids improve the outcomes of patients undergoing organ transplantation [7]. These reports were prepared by the Tufts-New England Medical Center Evidence-based Practice Center (Tufts EPC) [1,2,3,4], the University of Ottawa Evidence-based Practice Center at the University of Ottawa, Canada (Ottawa EPC) [5], and the Southern California/RAND Evidence-based Practice Center in Los Angeles (RAND EPC) [6,7].

Summary of key findings

- The polyunsaturated fatty acids alpha-linolenic acid (ALA) and linoleic acid (LA) must come from the diet because they cannot be made by the body. ALA, an omega-3 fatty acid, is converted in the body to the fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). LA, an omega-6 fatty acid, is converted to the fatty acid arachidonic acid (AA).
- Most American diets provide more than 10 times as much omega-6 than omega-3 fatty acids. There is general agreement that individuals should consume more omega-3 and less omega-6 fatty acids to promote good health. Good sources of ALA are leafy green vegetables, nuts, and vegetable oils such as canola, soy, and especially flaxseed. Good sources of EPA and DHA are fish and organ meats. LA is found in many foods, including meat, vegetable oils (e.g., safflower, sunflower, corn, soy), and processed foods made with these oils.
- EPA and DHA are metabolized through the same biochemical pathways as AA. EPA and AA are precursors for hormone-like agents known as eicosanoids. It is not known whether a desirable ratio of omega-6 to omega-3 fatty acids exists or to what extent high intakes of omega-6 fatty acids interfere with any benefits of omega-3 fatty acid consumption.
- Impact on cardiovascular disease: According to both primary and secondary prevention studies, consumption of omega-3 fatty acids, fish, and fish oil reduces all-cause mortality and various CVD outcomes such as sudden death, cardiac death, and myocardial infarction. The evidence is strongest for fish and fish oil supplements.
- Impact on heart function: Animal and isolated organ/cell culture studies demonstrate that omega-3 fatty acids affect cellular functions involved in ensuring a normal heart rate and coronary blood flow.

- Impact on CVD risk factors: Fish oils can lower blood triglyceride levels in a dose-dependent manner. Fish oils have a very small beneficial effect on blood pressure and possible beneficial effects on coronary artery restenosis after angioplasty and exercise capacity in patients with coronary atherosclerosis.
- Impact on asthma: No conclusions could be drawn about the value of omega-3 fatty acid supplements in the prevention or treatment of asthma for adults or children other than the fact that they have an acceptable safety profile.
- Impact on other conditions: Omega-3 fatty acids can reduce joint tenderness and need for corticosteroid drugs in rheumatoid arthritis. Data are insufficient to support conclusions about the effects of omega-3 fatty acids on inflammatory bowel disease, renal disease, systemic lupus erythematosus, bone density, and diabetes.
- Impact on cognitive function: The quantity and strength of evidence is inadequate to conclude that omega-3 fatty acids protect cognitive function with aging or the incidence or clinical progression of dementia (including Alzheimer's disease), multiple sclerosis, and other neurological diseases.
- Impact on organ transplantation: No conclusive evidence suggests specific benefits of omega-3 fatty acid supplementation on any outcome in any form of organ transplantation. However, available studies are small, have methodological problems, and may not fully apply to current transplantation procedures.
- Safety: Adverse events related to consumption of fish-oil or ALA supplements are generally minor and typically gastrointestinal in nature (such as diarrhea). They can usually be eliminated by reducing the dose or discontinuing the supplement.
- Conclusion: The health effects of omega-3 fatty acids require further investigation. Each report provides recommendations on specific research needs and how to improve the quality of future studies.

Background information about omega-3 and omega-6 fatty acids & their known functions

There are two major classes of polyunsaturated fatty acids (PUFAs) -- the omega-3 and the omega-6 fatty acids -- distinguished by their chemical structure. Only the fatty acids alpha-linolenic acid (ALA) and linoleic acid (LA) must come from the diet because they cannot be made by the body. ALA, an omega-3 fatty acid, is converted in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA also occur naturally in some foods. LA, an omega-6 fatty acid, is converted in the body to arachidonic acid (AA). Both EPA and DHA are metabolized through the same biochemical pathways as AA. Studies show that omega-3 fatty acids in general decrease triglyceride and very-low-density lipoprotein blood levels in hyperlipidemic individuals but may increase or have no effect on low-density lipoprotein (LDL) levels.

Both AA and EPA are further metabolized to produce hormone-like agents called eicosanoids, which include prostaglandins, thromboxanes, and leukotrienes. Eicosanoids regulate fundamental physiological processes such as cell division and growth, blood clotting, muscle activity, secretion of digestive juices and hormones, and movement of substances like calcium into and out of cells. However, AA and EPA lead to the production of different subgroups of eicosanoids with sometimes opposing effects. Eicosanoids formed from AA (particularly the series-2 prostaglandins and series-4 leukotrienes) are released in the body in response to injury, infection, stress, or certain diseases. They increase platelet aggregation and enhance vasoconstriction and the synthesis of substances involved with the inflammatory process. Eicosanoids derived from EPA (particularly the series-3 prostaglandins), in contrast, decrease excessive series-2 prostaglandin production. As a result, adequate production of EPA-derived series-3 prostaglandins may help protect individuals against heart attacks and strokes as well as certain inflammatory diseases such as arthritis, systemic lupus erythematosus, and asthma.

The omega-3 fatty acid DHA, while not involved in eicosanoid formation, is the major polyunsaturated fatty acid found in the brain and is important for brain development and function. Synapses are rich in DHA, which suggests that this fatty acid is involved in signal transmission along neurons. DHA is also required to produce one member of a family of compounds called resolvins that participate in the body's response to inflammation in the brain. The DHA-derived resolvin in particular helps to reduce inflammation brought about by ischemic insults (reductions in blood flow). (EPA also helps to temper inflammatory responses by decreasing production of proinflammatory compounds such as cytokines.)

Most American diets provide at least 10 times more omega-6 than omega-3 fatty acids. There is now general scientific agreement that individuals should consume more omega-3 and fewer omega-6 fatty acids for good health. It is not known, however, whether a desirable ratio of omega-6 to omega-3 fatty acids exists for the diet or to what extent high intakes of omega-6 fatty acids interfere with any benefits of omega-3 fatty acid consumption. Tufts EPC investigators reviewed the Third National Health and Nutrition Examination Survey (NHANES III; 1988-1994) database to examine intakes of omega-3 fatty acids in the United States. They found that men consumed significantly less ALA than women, adults consumed more than children, and those with a history of CVD consumed less than those without CVD (when energy intake was taken into account in the analysis). On any given day, only 25% of the population reported consuming any EPA or DHA. Average daily intakes were 14 g LA, 1.33 g ALA, 0.04 g EPA, and 0.07 g DHA.

ALA is present in leafy green vegetables, nuts, vegetable oils such as canola and soy, and especially in flaxseed and flaxseed oil. Good sources of EPA and DHA are fish (both finfish and shellfish and their oils and eggs) and organ meats. LA is found in many foods consumed by Americans,

including meat, vegetable oils (e.g., safflower, sunflower, corn, soy), and processed foods made with these oils. The Institute of Medicine has established Adequate Intakes for ALA and LA (1.1-1.6 g/day and 11-17 g/day, respectively, for adults) but not for EPA and DHA.

Products available

Omega-3 fatty acids are found in a variety of dietary supplements. For example, products containing flaxseed oil provide ALA, fish-oil supplements provide EPA and DHA, and algal oils provide a vegetarian source of DHA.

Omega-3 fatty acids for cardiovascular health and disease [1-3]

Epidemiological studies first published in the late 1970s noted relatively low cardiovascular mortality in populations such as Eskimos with high fish consumption. The apparent health benefits of fish are explained, at least in part, by the EPA and DHA they contain. Since these early studies, hundreds of observational and clinical trials have been conducted to evaluate the effects of EPA and DHA from marine sources and ALA from plant sources on CVD and its many risk factors and intermediate markers and to understand the potential benefits of increased intakes of omega-3 fatty acids.

The three reports by the Tufts EPC focused on different areas of research concerning this relationship between omega-3 fatty acids and cardiovascular health and disease and involved systematic reviews of the available scientific-medical literature. The first report focused on whole animal and isolated organ and cell culture studies to assess the effects of omega-3 fatty acids on arrhythmogenic mechanisms and outcomes. The second assessed the effects of EPA, DHA, and ALA on various CVD risk factors and intermediate markers of CVD in healthy people and people with dyslipidemia, diabetes, or known CVD. The third reviewed experimental and observational studies that investigated the effect of dietary or supplemental omega-3 fatty acids on specific clinical CVD outcomes (e.g., myocardial infarction and stroke) and whether these substances can play a role in the primary or secondary prevention of these outcomes.

Animal and isolated organ/cell culture studies [1]

A systematic review and screening of the literature identified 86 studies that met inclusion criteria and provided appropriate data. Of the 26 studies on living animals, a meta-analysis of 13 studies (with rats and monkeys) that compared the antiarrhythmic effects of ALA or fish oil with omega-6 fatty acids showed that fish-oil supplements (but not ALA) significantly reduced risk of death, ventricular tachycardia, and ventricular fibrillation. Since the majority of these studies were conducted by one research group, studies need to be repeated in other laboratories to confirm these results.

Another 60 studies evaluated the effects of omega-3 fatty acids on isolated organs and cell cultures. Seven of them reported that EPA and DHA (and in one instance ALA) protected against spontaneous or induced arrhythmias in both rat and guinea pig models. In the presence of various arrhythmogenic agents and across the species studied, omega-3 fatty acids consistently decreased the contraction rate and thereby had a protective effect compared with other substances, including placebos, but studies that did not administer an arrhythmogenic agent showed inconsistent results.

Conclusions cannot be drawn about the biochemical or physiological mechanisms that explain the potential antiarrhythmogenic effects of omega-3 fatty acids. These fatty acids affect cell functions (such as the movement of ions into and out of the cell) that are involved in cardiac electrophysiology to ensure a normal heart rate and coronary blood flow.

Cardiovascular risk factors and intermediate markers of CVD [2]

Many proposed risk factors for, and intermediate markers of, CVD exist. One report addressed the following risk factors and their relationship to omega-3 fatty acids in adults: total, LDL, and high density lipoprotein (HDL) cholesterol; triglycerides; lipoprotein (a); apolipoprotein (apo) A1; apo B; apo B-100 and LDL apo B; systolic and diastolic blood pressure; fasting insulin; C-reactive protein; fibrinogen; blood clotting factors VII, VIII, and von Willebrand factor; and platelet aggregation. The intermediate markers of CVD reviewed were coronary artery restenosis after angioplasty, carotid artery intima-media thickness, exercise tolerance testing, and heart rate variability. The literature review excluded studies of children, studies of daily omega-3 fatty acid intakes greater than 6 g/day, and studies less than 4 weeks long. A total of 123 articles that meet final eligibility criteria were reviewed regarding 23 potential risk factors and intermediate markers of CVD and tissue levels of omega-3 fatty acids. For most outcomes of interest, analysis was confined to the largest randomized trials.

Overall, strong evidence showed that fish-oil supplements had a substantial and beneficial effect on triglycerides that was greater with larger intakes of fish oil; most studies reported a net decrease of about 10-33%. There is also evidence of a very small beneficial effect of fish oils on blood pressure and possible beneficial effects on coronary artery restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and heart rate variability (particularly in patients with recent myocardial infarctions). No consistent beneficial effects were apparent for the other CVD risk factors or intermediate markers analyzed. Regarding concerns that glucose tolerance might be adversely affected by omega-3 fatty acids, there was no consistent evidence of a detrimental effect.

Meta-regression analysis of 50 trials showed that the dose of omega-3 fatty acids consumed was related to changes in EPA and DHA levels -- as plasma or serum phospholipids, platelet phospholipids, or in erythrocyte membranes -- without the influence of other factors. Supplementing the diet with 1-g of EPA and/or DHA resulted in approximately a 1% increase in the level of EPA and DHA and also to increases in granulocyte and monocyte membrane phospholipid levels. Few data are available, however, on how the effect of omega-3 fatty acids on CVD risk factors and intermediate

markers differs depending on people's underlying health status and risk of CVD, amount of omega-3 fatty acids consumed, duration of consumption, or source or type of these fatty acids. In particular, the potential effects of ALA are unknown.

Cardiovascular disease [3]

One report examined how dietary or supplemental omega-3 fatty acids affect specific CVD outcomes such as myocardial infarction and stroke and investigated whether these fatty acids can play a role in the primary and secondary prevention of these outcomes. A systematic review of the literature and subsequent screening identified 39 studies that met the investigators' inclusion criteria for reporting mortality or CVD clinical outcomes with a follow-up of at least one year. The primary prevention studies included 22 prospective cohort studies and only one randomized, controlled trial (RCT); they were conducted in countries around the world, most cohorts had several thousand subjects, and studies lasted from 4 to 30 years. The secondary prevention studies, in contrast, consisted of 11 RCTs and one prospective cohort study that reported outcomes on CVD populations; they included over 16,000 patients and lasted from 1.5 to 5 years.

Overall, evidence from both the primary and secondary prevention studies supports the hypothesis that consumption of omega-3 fatty acids, fish, and fish oil reduces all-cause mortality and various CVD outcomes such as sudden death, cardiac death, and myocardial infarction. The evidence is strongest for fish or fish oil whereas the potential effects of ALA are largely unknown and the relative effects of ALA versus fish oil are not well defined. In the only RCT that directly compared ALA and fish oil, both treatments reduced CVD outcome. No consistent differences in the effects of omega-3 fatty acids on CVD outcomes were found between men and women, largely because the proportion of women in RCTs was small and data from men and women were not analyzed separately to address any differences. Data were also insufficient to determine the optimal quantity and type of omega-3 fatty acids to consume or to identify an optimal ratio of omega-3 to omega-6 fatty acid intake, if one in fact exists.

The lessons to be drawn from all these studies to date regarding use of omega-3 fatty acids for preventing and treating CVD are not completely clear. Because the studies involved a variety of methods of estimating fish or omega-3 fatty acid intake, background diets, background risk for heart disease, settings, and methods for reporting results, the validity of applying the results of studies conducted outside the United States to the U.S. population is uncertain. Furthermore, dietary intervention trials are limited by the multiple and complex dietary changes in the trials that make it difficult to distinguish among components and determine which specific components or combinations of these diets are most beneficial. For example, the different types of fish consumed and the method of food preparation may cause different effects.

Omega-3 fatty acids for asthma [4]

Asthma is a major public health concern for Americans. In 1987 it was hypothesized that the low incidence of asthma among Eskimos resulted from their high intakes of oily fish rich in EPA and DHA. Basic research suggests that omega-3 fatty acids may affect asthma because they influence substances that are part of the inflammatory process involved with asthma, such as the series-2 prostaglandin PGE_2.

The Ottawa EPC conducted a comprehensive search of the published and unpublished scientific-medical literature. Its screening process identified 31 reports describing 26 studies. The primary outcome measure evaluated was the forced expiratory volume in one second, considered the best available method to assess pulmonary function. It was not possible to conduct a meta-analysis with the RCTs because of problems and limitations such as flawed designs, missing data, and incompatible study variables; most were small and lacked the ability to detect a statistical difference between the treatments, and inclusion and exclusion criteria were rarely reported.

Conclusions could not be made about the value of omega-3 fatty acid supplements in asthma for adults or children beyond that they have an acceptable safety profile. The evaluation of ten RCTs and nine other studies found the results to be too inconsistent and of limited applicability to larger groups of people to conclude that these supplements are an efficacious adjuvant or monotherapy. In some cases, asthma medications used by the subjects may have prevented the identification of any benefits from the omega-3 supplements. No other characteristics of the treatment (such as the type of fatty acid used, specific source, daily dose, and intervention length) were found to improve respiratory outcomes. As to whether omega-3 fatty acids influence substances that are part of the inflammatory process, such as PGE_2, the 11 relevant studies were insufficient to address this issue because of small sample sizes and differing methodologies.

Whether omega-3 fatty acids are effective in the primary prevention of asthma is unknown. Four observational studies in children support a positive association for dietary patterns that include all fish or oily fish, but a prospective study of adult nurses found no association between asthma onset and dietary fish intake. One RCT is evaluating the relationship in neonates at risk for asthma whose intake of omega-3 fatty acids or placebo was initiated before birth. Its interim results show little benefit from the supplement, though 18 months is probably too early in life to reliably identify asthma.

Omega-3 fatty acids for other diseases [5]

The RAND EPC conducted a comprehensive search of published and unpublished scientific-medical literature on the health effects of omega-3 fatty acids in type II diabetes and metabolic syndrome, inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and bone density/osteoporosis. Only articles that reported the results of RCTs or controlled clinical trials were included except for observational studies of bone mineral status. In all, 83 articles met the inclusion criteria, 82 of which were RCTs. Overall, the data were insufficient to draw conclusions about the value of omega-3 fatty acids for these medical problems with the exception of rheumatoid arthritis.

Type II diabetes and metabolic syndrome

Eighteen of the 34 RCTs whose subjects had type II diabetes or metabolic syndrome provided sufficient statistics to be included in a meta-analysis.

The analysis found that omega-3 fatty acids had a favorable effect on triglyceride levels when compared with placebo but had no effect on total, LDL, or HDL cholesterol; fasting blood sugar; or glycosylated hemoglobin. A qualitative analysis of 4 studies concluded that omega-3 fatty acids had no effect on plasma insulin or insulin resistance in subjects with either disorder.

Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
In the 13 studies that reported outcomes in patients with inflammatory bowel disease, omega-3 fatty acids had variable effects on assessment scores (clinical, sigmoidoscopic, and histologic), induced remission, and relapse rates. For ulcerative colitis, omega-3 fatty acids had no effect on the relative risk of relapse in a meta-analysis of three studies. The requirement for corticosteroids among patients receiving omega-3 fatty acids relative to placebo was not significantly reduced in two studies. No studies evaluated the effect of omega-3 fatty acids on the requirements for other immunosuppressive medications.

Rheumatoid arthritis
A meta-analysis of nine studies of patients with rheumatoid arthritis concluded that omega-3 fatty acids had no effect on patients' reports of pain and disease severity, swollen joint count, or erythrocyte sedimentation rate (a measure of disease activity). However, an earlier meta-analysis found that the omega-3 fatty acids produced a statistically significant improvement in tender joint count as compared with placebo. A qualitative analysis of seven studies that assessed the effect of omega-3 fatty acids on anti-inflammatory drug or corticosteroid requirements found that six demonstrated reduced requirements. No studies assessed how the supplements affected requirements for disease-modifying antirheumatic drugs and no studies used a composite score that incorporated both subjective and objective measures of disease activity. Overall, omega-3 fatty acids appear to reduce tender joint counts in individuals with rheumatoid arthritis and may reduce requirements for corticosteroids. The studies do not demonstrate an effect of the supplements on other clinical outcomes.

Renal disease
A qualitative analysis of nine studies assessing the effects of omega-3 fatty acids in renal disease concluded that the supplements had various effects on serum creatinine and creatinine clearance but no effect on the progression to end-stage renal disease. The one study that assessed hemodialysis graft patency found graft patency to be significantly better with fish oil than placebo. No studies assessed whether omega-3 fatty acids altered requirements for corticosteroids.

Systemic lupus erythematosus
A qualitative analysis of the three studies that assessed the effects of omega-3 fatty acids in systemic lupus erythematosus found variable effects on disease activity. No study assessed their effect on damage or patient perceptions of the severity of their disease. Omega-3 fatty acids had no effect on corticosteroid requirements in one study, but no study assessed how these supplements affected requirements for other immunosuppressive drugs. No study used both subjective and objective measures to study disease activity.

Bone density/osteoporosis
A qualitative analysis of five studies described in four reports found variable effects of omega-3 fatty acids on bone density. No studies were identified that assessed their effects on fractures.

Omega-3 fatty acids and cognitive function, dementia, and neurological diseases [6]

Omega-3 fatty acids appear to be important in brain development and function. Their effects on cognitive function in normal aging, incidence and treatment of dementia, incidence of several neurological diseases, and progression of multiple sclerosis were evaluated. A comprehensive search of the published and unpublished scientific-medical literature identified 12 studies that met inclusion criteria.

Cognitive function in normal aging and dementia
In the one cohort study that assessed the effects of omega-3 fatty acids on cognitive function with normal aging, fish consumption was only weakly associated with a reduced risk of cognitive impairment and had no association with cognitive decline over time; omega-3 fatty acid consumption was not associated with either outcome. Three prospective cohort studies evaluated the effects of these compounds on the incidence of dementia. Fish consumption was associated with a significant reduction in the incidence of non-Alzheimer's dementia in only one study. In all three, however, fish consumption was linked to a reduced risk of Alzheimer's dementia but was statistically significant in only one study. Total omega-3 fatty acid consumption and consumption of DHA (but not ALA or EPA) were associated with a significant reduction in the incidence of Alzheimer's disease. In the one RCT that assessed the effects of omega-3 fatty acids for the treatment of dementia, DHA produced a small improvement in scores on a dementia rating scale, but the sample size was small and the study was of poor quality.

Multiple sclerosis and other neurological diseases
Two studies (one cohort and one case control) that assessed the association between omega-3 fatty acid intake and incidence of multiple sclerosis found no significant results. In three studies that evaluated omega-3 fatty acid intake on disease progression, the RCT found no effects on disability or relapse rates, though the two single-arm open-label trials reported a significant reduction in disability (with one also reporting improvement on an index of disease progression).

Regarding other neurological diseases, one cohort study assessed the association between consumption of omega-3 fatty acids (from fish, ALA, EPA, or DHA) and risk for Parkinson's disease but found no significant associations. One case-control study found a significant association between maternal fish consumption at least once weekly throughout pregnancy and a lower risk of cerebral palsy in the offspring.

The quantity and strength of evidence for the effects of omega-3 fatty acids on cognitive function and decline, dementia, and neurological diseases vary greatly. Given the overall small number of studies and generally poor quality of clinical trials, substantive conclusions about the value of these compounds for these conditions cannot be drawn.

Omega-3 fatty acids for organ transplantation [7]

Several laboratory, animal, and human studies suggest that omega-3 fatty acids from fish oil may improve outcomes in organ transplantation (e.g., decrease rejection; reduce hyperlipidemia, hypertension, and blood viscosity; and decrease the toxicity of the immunosuppressive agent cyclosporin A). The Tufts EPC systematically identified studies of human subjects who underwent transplantation and received a quantifiable amount of omega-3 fatty acids. A total of 31 studies were included in the review pertaining to transplantation of the kidney (23), heart (6), liver (1), and bone marrow (1). All but one study used fish-oil supplements at doses ranging from 1.2 to 5.4 g/day EPA plus DHA, though in most the daily dose was 2-3 g.

No conclusive evidence was found suggesting specific benefits of omega-3 fatty acid supplementation on any outcome evaluated in any form of transplantation. The one possible exception was a reduction in triglyceride levels in patients who underwent kidney transplantation, which is consistent with the effects of omega-3 fatty acids for other conditions. The supplements did not cause clinically important interactions with cyclosporin A.

The quantity and quality of the evidence and its applicability to current transplantation procedures were limited. All studies were small and had methodological problems, such as the rigor with which endpoints were defined and measured, and most studies were not recent. Because the technology for transplantation continues to improve, whether fish-oil supplementation is beneficial with current procedures is uncertain. Furthermore, in all studies the supplements were begun after transplantation. Because it may take up to three weeks for omega-3 fatty acids to affect cytokine production, supplementation before the transplants might have influenced the outcomes.

Safety aspects of omega-3 fatty acids [3]

The Tufts EPC reviewed 148 studies to evaluate adverse events-not including fishy aftertaste-from the use of omega-3 fatty acid supplements (typically fish oils). More than half (77) reported that no adverse events had occurred. In total, about 10,000 subjects had taken these supplements in various forms and dosages ranging from 0.3 to 8 g/day for at least one week to more than seven years. Most studies were small, with a few dozen subjects receiving supplements for less than six months.

In general, side effects were minor, primarily gastrointestinal in nature (such as diarrhea), and reported by fewer than 7% of subjects. The supplements were not associated with serious adverse events such as death, life-threatening illness, significant disability, or handicap. Omega-3 fatty acids did not affect the frequency of bleeding events. However, several cases of clinical bleeding in two RCTs were reported where patients also took warfarin or aspirin daily; the bleeding (e.g., at the site of a wound or into the gastrointestinal tract) was typically mild.

The Tufts EPC concluded that adverse events related to consumption of fish-oil or ALA supplements appear to be minor and can be managed by reducing the dose or discontinuing the supplement. It noted, however, that adverse event data are incomplete because many studies did not adequately report this information, especially for subjects who withdrew before study completion.

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Effect of n−3 PUFA supplementation on cognitive function throughout the life span from infancy to old age: a systematic review and meta-analysis of randomized controlled trials[1–4]

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ABSTRACT

Background: n−3 PUFAs play an important role in cognitive function.

Objective: The objective was to investigate the effect of n−3 PUFA supplements on cognitive development, function, and decline throughout the life span.

Design: The study included randomized controlled trials and provided ≥3 mo of treatment. Potential studies were independently screened in duplicate, and study characteristics and outcomes were extracted. A meta-analysis was performed by using fixed- or random-effects models. The results are presented as standardized mean differences (SMDs) with 95% CIs.

Results: Of the 3692 citations retrieved, 34 studies of a total of 12,999 participants (1031 infants, 1517 children, 3657 adults, and 6794 elderly individuals) were included. Compared with placebo, n−3 PUFA supplements significantly improved the cognitive development in infants, including the Mental Development Index (SMD: 0.33; 95% CI: 0.15, 0.52), the Psychomotor Development Index (0.27; 95% CI: 0.09, 0.45), and language (0.27; 95% CI: 0.13, 0.42), motor (0.29; 95% CI: 0.14, 0.43), and cognitive (0.31; 95% CI: 0.16, 0.45) abilities. However, n−3 PUFAs did not promote cognitive function in terms of composite memory, executive function, and processing speed domains in children, adults, and the elderly, except for the attention domain. No association was found between n−3 PUFA intake and improvements in cognitive performance in terms of recognition, immediate and delayed word recall, digit span backward and forward tests, rapid visual information processing, verbal fluency, and simple and choice reaction times. In addition, n−3 PUFA supplements were not associated with improvements in cognitive decline or with any effects on Alzheimer disease in elderly people.

Conclusions: n−3 PUFA supplements may significantly improve cognitive development in infants but do not improve cognitive performance in children, adults, or the elderly. n−3 PUFA intake, especially that of DHA supplements, may benefit cognitive development during infancy. *Am J Clin Nutr* doi: 10.3945/ajcn.114.095315.

Keywords cognitive function, infancy, life span, meta-analysis, n–3 polyunsaturated fatty acid

INTRODUCTION

Cognition refers to a group of mental processes, including attention, working memory, language production and comprehension, learning, explanation, problem responses, and decision making. The global health burden of human cognitive decline and neurological disorders has surpassed that of both cardiovascular disease and cancer (1, 2). PUFAs are essential nutrients for humans and cannot be synthesized de novo in mammals (3). The Western diet has generally been low in fish and other sources of n−3 PUFAs, which leads to low blood concentrations of these fatty acids and an imbalance of dietary fatty acids during the past several decades (4). The n−3 PUFA supplements may become an alternative source for the dietary n−6/n−3 PUFA balance and health promotion. Thus, the role of n−3 PUFA supplementation in improving cognitive function has recently become a clinical focus (3, 5). However, related clinical trials have reported different outcomes at different age stages and have thus generated considerable controversy. Although there is conflicting clinical evidence regarding the benefits of n−3 PUFAs for the brain and cognitive function, it is thought that deficiencies in n−3 PUFAs have harmful effects on brain development; dietary supplementation of n−3 PUFAs may therefore be beneficial (6, 7). Clinical trials have suggested that n−3 PUFAs significantly affect prenatal neurodevelopment; however, such a cognitive-enhancing effect might diminish postnatally with maturation, because no research on child populations has clearly tied dietary n−3 PUFAs to improved cognitive skills (8, 9). Furthermore, evidence from clinical studies indicates that n−3 PUFAs may have therapeutic potential for mild cognitive impairment associated with neurodegenerative disorders such as Alzheimer disease (AD)[5] (10).

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[3] Supplemental Methods, Supplemental Tables 1–10, and Supplemental Figures 1–13 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[5] Abbreviations used: AD, Alzheimer disease; ADAS-Cog, Cognitive Subscale of the Alzheimer Disease Assessment Scale; LCPUFA, long-chain PUFA; MDI, Mental Development Index; MMSE, Mini-Mental State Examination; PDI, Psychomotor Development Index; RCT, randomized controlled trial; SMD, standardized mean difference.

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The controversial results have generated widespread confusion in everyday clinical practice regarding whether to use n−3 PUFA agents for cognitive protection in populations of different ages. Several epidemiologic studies have shown an explicit association between the intake of n−3 PUFA–supplemented formula and cognitive development in infants (11–13). Many randomized controlled trials (RCTs) have described the role of n−3 PUFAs in cognitive functions among children and adults (14–20). However, others have shown no effects on the prevention of cognitive decline and AD (21–23). Previous systematic reviews and meta-analyses did not fully address the overall effect of n−3 PUFAs on cognition and thus reported conflicting findings. Reasons may include the use of single outcome, data from both RCTs and observational findings, the use of n−6 PUFAs, inclusion of RCTs with a short intervention period, inclusion of populations only of a specific age, or exclusion of healthy individuals/inclusion of only patients with cognitive decline (24–28). In the current study, we set out to conduct a large-scale systematic review and meta-analysis of RCTs to summarize the effect of n−3 PUFAs on cognitive performance outcomes throughout the life span, extending from infants to the elderly.

MATERIALS AND METHODS

Literature search

A systematic literature search (1950–May 2014) of PubMed, Embase, and the Cochrane Library Central Register of Controlled Trials was performed to identify all published RCTs that studied the effect of n−3 PUFA supplementation, compared with placebo, on cognitive function. RCTs investigating the effect of n−3 PUFA–supplemented formula (compared with general formula feeding) on cognitive development in infants were also included. The search was not restricted to any language or publication date. Keywords used for the search comprised synonyms and abbreviations of *n−3 polyunsaturated fatty acid*, *docosahexaenoic acid*, *eicosapentaenoic acid*, *cognition*, *cognitive decline,* and *Alzheimer's disease* (**Supplemental Methods 1**). Trials were eligible if they were RCTs and implemented in primary or secondary outcome settings; n−3 PUFAs could be administered via formula or supplements. We initially screened 3692 articles using the literature search strategy. A total of 1780 records were selected after removing 1912 duplicate records. Of these articles, 331 were identified for further review based on the exclusion of 1449 records, i.e., unrelated reports, reviews, and cell or animal studies. After 297 studies were excluded, a total of 34 RCTs fit our inclusion criteria and were used for the meta-analysis (**Figure 1**).

Study selection and data extraction

Two investigators (JJ and QL) reviewed the literature and independently identified studies for possible inclusion. Disagreements were resolved by negotiation and consensus. To ensure efficacy in terms of cognitive function, we excluded studies with the following characteristics: *1*) an intervention duration of <3 mo—an insufficient time for n−3 PUFA treatment; *2*) inclusion of a multinutrient intervention besides n−3 PUFAs (e.g., vitamins and phytochemicals); *3*) a treatment mixed by n−6 PUFAs; and *4*) inclusion of an effect of an n−3 PUFA–rich diet (e.g., a fish-heavy diet). The selected studies fulfilled the following criteria: *1*) an intervention group that received at least one dose level of n−3 PUFA treatment and *2*) a control group that received appropriate placebo treatment. Populations from selected studies were not permitted to have had exposure to similar PUFA treatments before the investigation, unless an adequate washout period was clearly specified. We then extracted information about the characteristics of the included studies, such as authors, publication year, countries from which the study populations originated, population age and female ratio, n−3 PUFA treatment, type of placebo control, treatment duration, outcome measures of cognitive performance, number of participants, funding sources, and information about potential sources of bias. The standardized mean differences (SMDs) and 95% CIs of outcomes were finally extracted for further data synthesis.

Outcome measures

The primary outcome of this systematic review was cognitive function throughout the life span. However, such an analysis should include measures of cognitive development in infants, cognitive performance in children, adults, the elderly, and possible cognitive decline in the elderly.

1) The Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development were taken as the primary outcomes during infancy (27, 29). To further evaluate cognition, language, motor, and cognitive abilities were considered as secondary outcomes.

2) Composite memory, executive function, attention, and processing speed were used as the representative cognitive domains and were regarded as the primary outcomes during the child, adult and the elderly stages of the life span (15, 26, 30). To further describe these domains, we also included other secondary outcomes, including recognition, immediate word recall, delayed word recall, digit span backward, digit span forward, the Stroop effect, rapid visual information processing, verbal fluency, simple reaction time, and choice reaction time (14–17, 31, 32).

3) The Mini-Mental State Examination (MMSE) result was used as a primary outcome to screen for cognitive decline in elderly people (4, 25, 33–35). Considering the prevalence of AD in cognitive decline, we chose the score of the Cognitive Subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog) as an additional secondary outcome (21, 23, 36).

Explanations and details of all above outcomes are available in **Supplemental Methods 2**. Data about the primary and secondary outcomes in all of the n−3 PUFA groups were included if multiple dose levels or multiple types of n−3 PUFAs were considered as the intervention. Whenever clinical trials referred to the same populations at different follow-up periods, we only used the population with the longest follow-up period to avoid data duplication.

Assessment of methodologic quality

Two authors (JJ and JC) independently assessed the risk of bias in included RCTs using the Cochrane Risk of Bias Tool (37). The

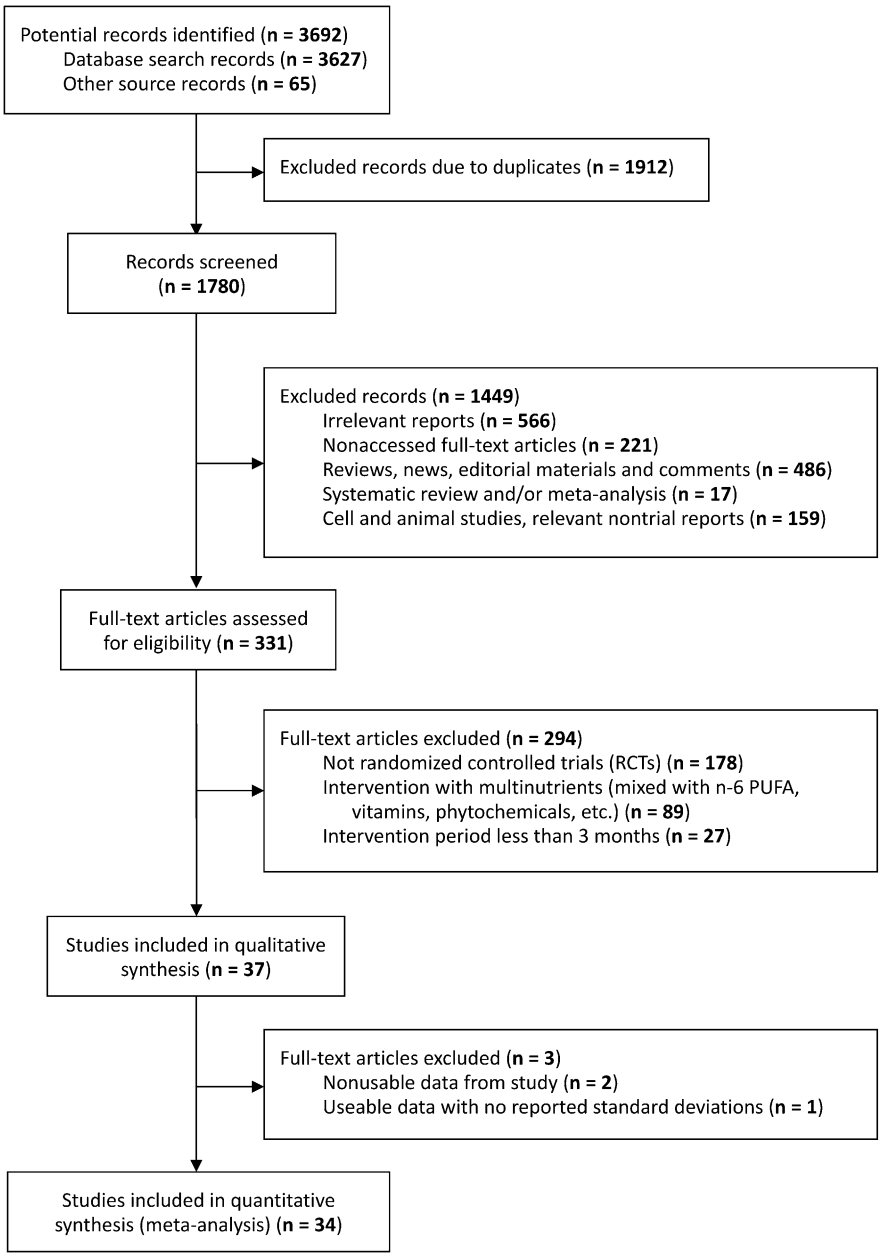

FIGURE 1 Flowchart of the selection of studies for the systematic review and meta-analysis.

domains used in the current systematic review pertained to randomization and allocation concealment (selection bias), blinding (performance and measurement bias), loss to follow-up and adherence to the intent-to-treat principle (attrition bias), and selective outcome publication (reporting bias). An acknowledged study quality score for evaluating RCTs (Jadad score) was also applied with a score of ≥3 indicating high quality.

Statistical analysis

SMDs were calculated as the mean difference in the change of cognitive function between the n−3 PUFA group and the placebo group, divided by the pooled SD, with an adjustment for small sample bias (Hedges *g*) (38). Hedges *g* provides a standardized estimate of effect size that is suitable for merging multiple cognitive tests in populations of varying sample sizes and has been widely used in a meta-analysis (26, 39). Of the included studies, several provided means ($m_{\text{treatment}}$ and m_{placebo}) and SDs ($SD_{\text{treatment}}$ and SD_{placebo}) at baseline and follow-up, but did not report the within-subject change in SD, which was required for the meta-analysis. Initially, we tried to contact the corresponding authors of these studies to obtain this unpublished data. However, we could not obtain responses from the authors in some cases and thus considered an imputation approach. In such situations, the $SD_{\text{follow-up–baseline}}$ of SMDs of the selected outcomes were estimated by merging the SDs reported at baseline and at the follow-up endpoint with the weighted mean correlation (Cor) between baseline and follow-up visits reported by other reports, thus weighted by the sample size of each trial, as expressed in the following equation (38, 40).

$$SD_{(follow-up-baseline)} = \sqrt{SD^2_{baseline} + SD^2_{follow-up} - (2 \times Cor_{(baseline,follow-up)} \times SD_{baseline} \times SD_{follow-up})} \quad (1)$$

To check the imputation effect on the precision of the current meta-analysis, we performed a sensitive analysis and compared the results of n−3 PUFA treatment effects using the above imputation with corresponding results using directly reported data without imputation. To investigate variances in cognitive function at different ages that may have been affected by n−3 PUFA treatment, we conducted a planned subgroup analysis to examine the effect of n−3 PUFA treatment on the following domains: *1*) primary outcomes, including composite memory, attention, and processing speed and *2*) secondary outcomes, including recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, and verbal fluency. When more than one treatment group (e.g., multiple treatment levels of n−3 PUFAs or multiple types of n−3 PUFA treatments) was used in an included study, the effect sizes for each group were individually evaluated and regarded as multiple treatment effects.

Study heterogeneity regarding comparisons of each cognitive function domain was assessed by using a Q statistic in the chi-square test, whereas the effect of heterogeneity was evaluated with an I^2 statistic (41). A significant Q statistic ($P \leq 0.05$ and/or $I^2 > 55\%$) indicates differences in study characteristics and high heterogeneity. In this situation, a meta-analysis using the random-effects model would be used to combine the study outcomes, assuming that studies were drawn from unequal populations and therefore accounting for variable underlying effects in the estimates of uncertainty (38). Otherwise, the fixed-effects model was used for the meta-analysis. Heterogeneity was also investigated by using subgroup analyses of outcomes in both children and adult groups and the elderly group. To investigate whether various study characteristics could explain the observed heterogeneity, meta-regression analyses (summarized as a β coefficient) were conducted by comparing effect sizes with selected study characteristics such as duration of n−3 PUFA treatment, dose levels of n−3 PUFAs, mean age, and percentage of female participants. The risk of small study effects was assessed by visualization of funnel plots (42), followed by the Egger's test (43). All statistical analyses and meta-analyses were performed with Stata software (version 11.0; StataCorp).

RESULTS

Literature search results and study characteristics

Of the 34 RCT articles retrieved, 7 articles investigated cognitive development in infants (567 in a treatment group vs. 464 in a control group) (11–13, 44–47); 15 articles investigated cognitive function in children and adults (2642 in a treatment group vs. 2532 in a control group) (9, 14, 16–19, 31, 48–55); and 12 articles investigated cognitive function, decline, and related diseases (e.g., AD) in elderly people (4213 in a treatment group vs. 2581 in a control group) (15, 20–23, 32, 36, 56–60). The demographic features and other characteristics of all the included trials are summarized in **Tables 1** and **2**. Of the 34 trials that were included in this analysis, 5 used DHA-supplemented infant formulas as the treatment, 7 used single n−3 PUFA supplements (DHA or ethyl-EPA) as the treatment, and 22 used combined mixed n−3 PUFA supplements as the treatment. Regarding the controls, 5 studies used commercial infant formula, 10 used olive oil, 4 used corn oil, 3 used mixed corn and soy oils, 8 used other oils, and 3 did not report details of the control group. The age of the participants throughout all of the trials ranged from birth to 86 y, which covers nearly the entire scale of the human life span. The duration of n−3 PUFA treatment ranged from 12 wk to 4 y. Of 11,968 individuals (infants not included), 6855 received a median intervention dose of 1 g/d (IQR: 0.6–1.74 g/d). Overall, 12,999 participants (52.5% female) were treated and followed up, for a median treatment duration of 6 mo (IQR: 4–11.1 mo).

TABLE 1
Summary of the characteristics of eligible RCTs[1]

	Eligible RCTs		
Characteristics	Infants	Children and adults	Elderly
No. of RCTs	7	15	12
Participants			
Total no.	1031	5174	6794
Median (IQR)	88 (54–182)	161 (94–352)	253 (52–581)
Publication year	2007 (2000–2012)[2]	2011 (2008–2012)	2010 (2008–2011)
Age	0.07 (0–18.1) mo	22.2 (9.0–30.5) y	71.4 (68.9–74.2) y
Female sex, %	47.3 (45.2–53.2)	64.0 (48.1–90.0)	51.5 (41.9–56.9)
Treatment duration, mo	7.9 (4.0–12.0)	4.5 (3.7–7.5)	6.1 (5.9–19.5)
n−3 PUFA dose[3]	0.35 (0.35–0.35)	0.9 (0.6–1.5)	1.4 (0.9–1.8)

[1]There was a total of 34 RCTs and a total of 12,999 participants. RCT, randomized controlled trial.
[2]Median; IQR in parentheses (all such values).
[3]The n−3 PUFA dose in infant RCT studies is presented as the percentage of total fatty acids supplemented in formula. The n−3 PUFA dose in all other categories is expressed as g/d. Two studies were excluded because n−3 PUFAs were administered as a capsule supplement (46, 47).

TABLE 2
Characteristics of the included RCTs[1]

Source (study name), country (ref)	Age; female sex, %	n−3 PUFA dose[2]	Control	Treatment duration	Outcome measures of cognitive performance	No. of RCT participants	Funding source
Infants (cognitive development)							
Birch et al., 2000, US (11)[3]	2.1 ± 1.0 d; T: 59%/C: 55%	DHA (0.35% of total fatty acids)	Commercial infant formula	17 wk	MDI, PDI, BRS, cognition, language, motor	T: 26/C: 26	Academy
Birch et al., 2007, US (44)[3,4]	2.1 ± 1.0 d; T: 59%/C: 55%	DHA (0.35% of total fatty acids)	Commercial infant formula	17 wk	Performance IQ, verbal IQ, full-scale IQ	T: 26/C: 26	Academy
Drover et al. (DIAMOND), 2011, US (12)	T1: 18.1 ± 0.2 mo/T2: 18.1 ± 0.2 mo/T3: 18.1 ± 0.2 mo/C: 18.1 ± 0.2 mo; T1: 45%/T2: 38%/T3: 46%/C: 50%	DHA (T1: 0.32% of total fatty acids; T2: 0.64% of total fatty acids; T3: 0.96% of total fatty acids)	Commercial infant formula	12 mo	MDI, PDI, BRS, cognition, language, motor	T1: 45/T2: 44/T3: 46/C: 46	Industry
Makrides et al., 2000, Australia (45)[3,4]	Birth; T: 48%/C: 48%	DHA (0.35% of total fatty acids)	Formula with no LCPUFA	34 wk	MDI, PDI	T: 27/C: 28	Academy and industry
Meldrum et al., 2012, Australia (46)	Birth; T: 48.4%/C: 48.5%	EPA (0.06 g/d); DHA (0.25 g/d)	Olive oil	6 mo	Cognition, language, motor, social emotion, adaptive behavior	T: 218/C: 202	Academy
Scott et al., 1998, US (13)[3,4]	T: 2.6 ± 1.9 d/C: 3.2 ± 2.5 d; T: 49%/C: 42%	DHA (0.20% of total fatty acids)	Commercial infant formula	12 mo	MDI, PDI	T1: 43/C:45	Academy and industry
Van der Merwe et al., 2013, Gambia (47)	T: 92.3 ± 4.25 d/C: 93.2 ± 4.22 d; T: 44%/C: 41%	EPA (0.3 g/d); DHA (0.2 g/d)	Olive oil	6 mo	Total intention, intentional solutions, inattention rate, mean look duration	T: 92/C: 91	Academy
Children and adults (cognitive function)							
Baumgartner et al., 2012, South Africa (14)[3]	T: 8.9 ± 1.3 y/C: 9.1 ± 1.4 y; T: 43%/C: 55%	EPA (0.046 g/d); DHA (0.24 g/d)	Medium-chain triglycerides	8.5 mo	Recognition, immediate word recall, delayed word recall, discrimination index	T: 81/C: 80	Academy
Cheatham et al., 2011, Denmark (48)[3]	T: 7.4 ± 1.5 y/C: 7.3 ± 1.4 y; T: 33.3%/C: 57.1%	EPA (0.62 g/d); DHA (0.79 g/d); others (0.09 g/d)	Olive oil	4 mo	Processing speed, Stroop effect, SDQ scores	T: 36/28	Academy
Dunstan et al., 2008, Australia (49)	T: 30.9 ± 3.7 y/C: 32.6 ± 3.6 y; T: 100%/C: 100%	EPA (1.1 g/d); DHA (2.2 g/d)	Olive oil	20 wk	Griffiths Mental Development Scale scores, Peabody Picture Vocabulary Test IIIA scores, Child Behavior Checklist scores	T: 52/C: 46	Academy
Helland et al., 2008, Norway (50)[5]	T: 29.7 ± 3.3 y/C: 28.6 ± 2.6 y; T: 100%/C: 100%	EPA (0.803 g/d); DHA (1.183 g/d); others (0.508 g/d)	Corn oil	8 mo	Kaufman Assessment Battery for Children scores	T: 175/C: 166	Academy
Jackson et al., 2012, UK (16)	T1: 22.74 ± 4.14 y/T2: 21.96 ± 3.66 y/C: 21.94 ± 3.46 y; T1: 60.9%/T2: 63.0%/C: 77.1%	T1: EPA (0.3 g/d) + DHA (0.2 g/d); T2: EPA (0.09 g/d) + DHA (0.45 g/d)	Olive oil	12 wk	Immediate word recall, delayed word recall, simple RT, choice RT, Stroop effect, verbal fluency, RT of working memory, Corsi blocks span, RT of 3-back task, recognition,	T1: 46/T2: 46/C: 48	Industry
Jackson et al., 2012, UK (17)	T1: 20.50 ± 2.02 y/T2: 19.95 ± 1.56 y/C: 21.35 ± 2.91 y; T1: 86.4%/T2: 86.4%/C: 68.2%	T1: EPA (0.09 g/d) + DHA (0.45 g/d); T2: EPA (0.18 g/d) + DHA (0.9 g/d)	Olive oil	12 wk	Corsi blocks span, RT of working memory, RT of 3-back task, simple RT, choice RT, Stroop effect	T1: 22/T2: 21/C: 22	Industry
Kirby et al., 2010, UK (51)	T: 9.17 ± 0.57 y/C: 9.08 ± 0.56 y; T: 52.6%/C: 50.8%	EPA (0.056 g/d); DHA (0.4 g/d)	Italian olive oil	16 wk	Digit span forward, digit span backward, word reading, spelling, SDQ scores	T: 225/C: 225	Industry

(Continued)

TABLE 2 (*Continued*)

Source (study name), country (ref)	Age; female sex, %	n−3 PUFA dose[2]	Control	Treatment duration	Outcome measures of cognitive performance	No. of RCT participants	Funding source
Makrides et al. (DOMInO), 2010, Australia (9)[5]	T: 28.9 ± 5.7 y/C: 28.9 ± 5.6 y; T: 100%/C: 100%	EPA (0.1 g/d); DHA (0.8 g/d)	Vegetable oil	19–40 wk	Cognition, language, motor, social emotion, adaptive behavior	T: 1197/C: 1202	Academy
Milte et al., 2012, Australia (52)	T1: 8.77 ± 1.76 y/T2: 8.89 ± 1.60 y/C: 9.14 ± 2.03 y; T1: 20%/T2: 25%/C: 17%	T1: EPA (1.109 g/d) + DHA (0.108 g/d); T2: EPA (0.264 g/d) + DHA (1.032 g/d)	Safflower oil	4 mo	Word reading, spelling, vocabulary, CPRS	T1: 31/T2: 29/C: 30	Academy
Osendarp et al., 2007, Australia and Indonesia (18)[3]	T: 8.8 ± 1.0 y/C: 8.5 ± 1.0 y; T: 45%/C: 39% (Australia) T: 8.1 ± 1.1 y/C: 8.1 ± 1.1 y; T: 52%/C: 50% (Indonesia)	T (Australia)/T (Indonesia): EPA (0.022 g/d) + DHA (0.088 g/d)	NR	12 mo	Composite memory, attention	T: 96/C: 102 (Australia); T: 97/C: 95 (Indonesia)	Industry
Puri et al., 2005, UK, US, Canada, and Australia (53)	T: 50 ± 9.3 y/C: 49 ± 9.0 y; T: 43%/C: 56%	Ethyl-EPA (2 g/d)	Liquid paraffin	12 mo	Total motor score 4 of UHDRS, verbal fluency, symbol digit, Stroop effect	T: 67/C: 68	Industry
Richardson et al., 2012, UK (31)	T: 103.7 ± 10.0 mo/C: 104.8 ± 10.1 mo; T: 46.7%/C: 47.3%	DHA (0.6 g/d)	Corn/soybean oil	16 wk	Digit span forward, digit span backward, word reading, CPRS, CTRS	T: 180/C: 182	Academy
Rogers et al., 2008, UK (54)	T: 38.0 ± 13.5 y/C: 38.2 ± 13.7 y; T: 78%/C: 76%	EPA (0.63 g/d); DHA (0.85 g/d)	Olive oil	12 wk	Simple RT, RT of lexical decision, RT of digit-symbol	T: 109/C: 109	Academy
Stonehouse et al., 2013, New Zealand (19)	T: 33.4 ± 7.6 y/C: 33.2 ± 7.90 y; T: 63%/C: 65%	DHA (1.16 g/d)	Sunflower oil	6 mo	Attention, processing speed, RT of attention, RT of working memory	T: 115/C: 113	Academy
Yi et al., 2011, US (55)	T: 24.4 ± 10.6 y/C: 25.6 ± 10.7 y; T: 100%/C: 100%	DHA (10 mg · kg^{-1} · d^{-1})	Mixture of soy and corn oils	4.5 mo	Processing speed, verbal ability, cognitive inhibition, cognitive flexibility	T: 17/C: 16	Academy
Elderly people (cognitive function and decline)							
Andreeva et al. (SU.FOL.OM3), 2011, (France) (56)[3]	T: 60.1 ± 8.7 y/C: 60.9 ± 8.9 y; T: 20.0%/C: 22.6%	EPA (0.4 g/d); DHA (0.2 g/d)	NR	48 mo	Composite memory	T: 633/C: 626	Academy and industry
Chiu et al., 2008 Chinese Taiwan (36)	T: 74.0 ± 8.9 y/C: 76.5 ± 9.3 y; T: 65.0%/C: 46.7%	EPA (1.08 g/d); DHA (0.72 g/d)	Olive oil esters	24 wk	MMSE, ADAS-Cog	T: 24/C: 22	Academy
Dangour et al. (OPAL), 2010, UK (15)	T: 74.7 ± 2.5 y/C: 74.6 ± 2.7 y; T: 46.6%/C: 43.4%	EPA (0.2 g/d); DHA (0.5 g/d)	Olive oil	24 mo	Composite memory, executive function, attention, processing speed, immediate word recall, delayed word recall, digit span forward, digit span backward, verbal fluency, simple RT, choice RT	T: 434/C: 433	Academy
Freund-Levi et al. (OmegAD), 2008, Sweden (57)	T: 72.6 ± 9.0 y/C: 72.9 ± 8.6 y; 57%/46%	EPA (0.6 g/d); DHA (1.72 g/d)	Corn oil	6 mo	Neuropsychiatric inventory	T: 103/C: 101	Academy and industry
Freund-Levi et al. (OmegAD), 2006, Sweden (21)	T: 72.6 ± 9.0 y/C: 72.9 ± 8.6 y; T: 57%/C: 46%	EPA (0.6 g/d); DHA (1.72 g/d)	Corn oil	6 mo	MMSE, ADAS-Cog, CDR sum of boxes	T: 103/C: 101	Academy and industry

(*Continued*)

TABLE 2 (*Continued*)

Source (study name), country (ref)	Age; female sex, %	n−3 PUFA dose[2]	Control	Treatment duration	Outcome measures of cognitive performance	No. of RCT participants	Funding source
Geleijnse et al., 2012, The Netherlands (58)	T1: 69.2 ± 5.4 y/T2: 69.1 ± 5.6 y/T3: 69.2 ± 5.6 y/C: 68.9 ± 5.4 y; T1: 3.0%/T2: 22.8%/T3: 21.8%/C: 20.0%	T1: EPA (0.24 g/d) + DHA (0.16 g/d); T2: ALA (2 g/d); T3: EPA (0.24 g/d) + DHA (0.16 g/d) + ALA (2 g/d)	Margarine	40 mo	MMSE	T1: 726/T2: 727/T3: 719/C: 739	Academy and industry
Johnson et al., 2008, US (59)[3]	T: 68.5 ± 4.9 y/C: 68.0 ± 3.8 y; T: 100%/C: 100%	DHA (0.8 g/d)	NR	4 mo	Recognition, digit span forward, digit span backward, Stroop effect	T: 14/C: 10	Academy
Lee et al., 2013, Malaysia (22)	T: 66.4 ± 5.1 y/C: 63.5 ± 3.0 y; T: 82.4%/C: 72.2%	EPA (0.45 g/d); DHA (1.29 g/d)	Corn oil	12 mo	Composite memory, executive function, attention, processing speed, MMSE, immediate word recall, delayed word recall	T: 18/C: 18	Academy
Quinn et al., 2010, US (23)	T: 76 ± 9.3 y/C: 76 ± 7.8 y; T: 47.1%/C: 59.8%	DHA (0.9–1.1 g/d)	Corn or soy oil	18 mo	MMSE, ADAS-Cog, CDR sum of boxes, neuropsychiatric inventory	T: 238/164	Academy
Sinn et al., 2012, Australia (32)	T1: 74.88 ± 5.06 y/T2: 74.22 ± 7.00 y/C: 73 ± 3.96 y; T1: 18%/T2: 28%/C: 53%	T1: EPA (1.67 g/d) + DHA (0.16 g/d); T2: EPA (0.40 g/d) + DHA (1.55 g/d)	Safflower oil	6 mo	Recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, verbal fluency	T1: 18/T2: 18/C: 18	Academy
van de Rest et al., 2008, The Netherlands (20)	T1: 69.5 ± 3.2 y/T2: 69.9 ± 3.4 y/C: 70.1 ± 3.7 y; T1: 45%/T2: 45%/C: 44%	T1: EPA (0.226 g/d) + DHA (0.176 g/d); T2: EPA (1.093 g/d) + DHA (0.847 g/d)	High–oleic acid sunflower oil	26 wk	Composite memory, executive function, attention, processing speed, recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, verbal fluency	100/96/106	Academy
Yurko-Mauro et al., 2010, US (60)	T: 70 ± 9.3 y/C: 70 ± 8.7 y; T: 56%/C: 60%	DHA (0.9 g/d)	Corn and soy oil	24 wk	Composite memory, MMSE, recognition, immediate word recall, delayed word recall	T: 242/C: 243	Industry

[1]ADAS-Cog, Cognitive Subscale of the Alzheimer's Disease Assessment Scale; BRS, Behavior Rating Scale; C, control; CDR, Clinical Dementia Rating; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; DIAMOND, DHA Intake And Measurement Of Neural Development; DOMInO, DHA to Optimize Mother Infant Outcome; IQ, intelligence quotient; LCPUFA, long-chain PUFA; MDI, Mental Development Index; MMSE, Mini-Mental State Examination; NR, not reported; OmegAD, Omega-3 and Alzheimer's Disease; OPAL, the Older People And n−3 Long-chain poly-unsaturated fatty acids; PDI, Psychomotor Development Index; RCT, randomized controlled trial; RT, reaction time; SDQ, Strengths and Difficulties Questionnaire; SU.FOL.OM3, SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids; T, treatment; UHDRS, Unified Huntington's Disease Rating Scale.

[2]All studies used n−3 PUFA supplements, except for some studies in infants that administered n−3 PUFA–supplemented formula.

[3]Participants from the irrelevant or other mixed-nutrient supplement treatment groups were excluded.

[4]Participants from the breast milk–fed groups were excluded.

[5]Participants were singleton pregnant women, and cognitive outcomes were measured in their children.

Six trials were graded as having a low risk of bias in all domains of the Cochrane Risk of Bias tool (**Supplemental Figures 1–3**) (14, 19, 20, 23, 46, 58). We realized that selective reporting was the most frequent deficiency in trials because one or more outcomes of interest in these trials were reported incompletely and could not be entered in a meta-analysis. The Jadad quality evaluation of included RCTs showed that the low quality was mainly ascribed to lack of adequate randomization and blind method details, although both methods were clearly mentioned in most of the trials (**Supplemental Table 1**).

Primary outcome measures of cognitive function

The meta-analysis of 7 infant trials showed that n−3 PUFA supplementation could significantly improve MDI and PDI, which are important outcome indexes of cognitive development in infants. The treatment effects on MDI and PDI between the n−3 PUFA treatment and control groups were SMDs of 0.33 (95% CI: 0.15, 0.52) and 0.27 (95% CI: 0.09, 0.45), respectively (**Figure 2**). Meanwhile, both effects were acceptably heterogeneous across trials (MDI: I^2 = 7.8%, P = 0.366; PDI: I^2 = 54.7%, P = 0.050; **Supplemental Table 2**).

For estimating cognitive performance in children, adults, and the elderly, we chose 4 acknowledged cognitive domains, including composite memory, executive function, attention, and processing speed as our primary outcomes, which are consistent with expert recommendations (30, 61). Our results showed that n−3 PUFA supplementation significantly improved the attention domain as a whole (SMD: 0.13; 95% CI: 0.01, 0.25). Considering the difference among population groups, we then conducted a subgroup analysis and observed the treatment effect, classified by age. Subgroup analysis showed that improvements in the attention domain were significant in the elderly (0.29; 95% CI: 0.10, 0.47), but not in children or adults (0.02; 95% CI: −0.14, 0.18) (**Figure 3**A). Furthermore, the treatment effect was significantly heterogeneous across studies (I^2 = 59.0%, P = 0.032), which may be generated by the differential effects in the subgroup of elderly people (I^2 = 68.5%, P = 0.042; Supplemental Table 2). Our results also indicated that n−3 PUFAs did not significantly improve the domains of composite memory (0.01; 95% CI: −0.06, 0.07), executive function (−0.03; 95% CI: −0.14, 0.08), and processing speed (−0.07; 95% CI: −0.16, 0.03) in either the overall or subgroup meta-analyses (Figure 3B and **Figure 4**A, B). To evaluate potential cognitive declines in the elderly, we investigated the results of the MMSE, which were not significantly affected by n−3 PUFA supplementation (0.04; 95% CI: −0.02, 0.10) with no heterogeneity across trials (I^2 = 0.0%, P = 0.882; **Figure 5** and Supplemental Table 2).

Secondary outcome measures of cognitive function

To further demonstrate the positive treatment effect of n−3 PUFAs in infant growth, we investigated the development of language, motor, and cognitive abilities by comparing brain development in the treated and control groups. Forest plots showed that infants receiving n−3 PUFA supplementation exhibited a significant improvement in all aspects of language (0.27; 95% CI: 0.13, 0.42), motor (0.29; 95% CI: 0.14, 0.43), and cognitive (0.31; 95% CI: 0.16, 0.45; **Supplemental Figure 4**) abilities. However, all of these effects remained highly heterogeneous across trials (language: I^2 = 75.5%, P = 0.003; motor: I^2 = 72.2%, P = 0.006; cognitive: I^2 = 63.1%, P = 0.028; **Supplemental Table 3**).

Because of the above positive effects, we were interested in obtaining more information about the effect of n−3 PUFAs on cognition in developing humans. We found positive effects on some (e.g., attention) but not all (e.g., composite memory, executive function, and processing speed) cognitive domains in children, adults and the elderly. To further understand this, we comprehensively investigated the treatment effect of n−3 PUFAs on representative secondary outcomes of cognitive performance in subjects in the included trials. Unfortunately, results of the meta-analysis and subgroup analyses did not show that n−3 PUFAs had any positive effects on cognitive function indexes, including recognition (0.01; 95% CI: −0.10, 0.12), immediate word recall (−0.02; 95% CI: −0.11, 0.06), delayed word recall (0.08; 95% CI: −0.01, 0.16), digit span forward (0.03; 95% CI: −0.06, 0.12), digit span backward (−0.03; 95% CI: −0.11, 0.06), Stroop effect (0.11; 95% CI: −0.02, 0.24), rapid visual information processing (0.13; 95% CI: −0.04, 0.30), verbal fluency (−0.08; 95% CI: −0.18, 0.02), simple reaction time (−0.05; 95% CI: −0.16, 0.06), and choice reaction time (0.07; 95% CI: −0.05, 0.18). However, a promising effect on the Stroop test was observed in children and adults (0.22; 95% CI: 0.04, 0.40) after comparison with the placebo group (**Supplemental Figures 5–10**). In addition, we found that n−3 PUFAs had no effect on the ADAS-Cog score (−0.03; 95% CI: −0.18, 0.13), which is a key outcome in evaluating the cognitive decline, especially that related to AD. This finding was consistent with our findings regarding the MMSE, which was the primary outcome in the elderly (**Supplemental Figure 11**). Furthermore, low or no heterogeneity for all of the above outcomes was observed across the included trials (Supplemental Table 3). Overall, in terms of the primary outcome measures, we concluded that n−3 PUFA supplementation may significantly improve cognitive development in infants; however, it does not appear to improve cognitive function in children, adults, and the elderly, nor does it prevent cognitive decline in the elderly.

Sensitivity analysis, evaluation of small study effects, and meta-regression

No significant heterogeneity was found for treatment effect in terms of the primary cognitive function outcomes, except for the attention domain in primary cognitive function outcomes. To further confirm such positive results for the attention domain and investigate the imputation effect on this statement, a relative sensitivity analysis was conducted. The reported data were directly used to generate SMDs of each primary and secondary outcome in children, adults, and the elderly (**Supplemental Tables 4** and **5**). The results indicated that all of the outcomes agreed with previously corresponding outcome measures, except the attention outcome. No significant amelioration effect of n−3 PUFAs on the attention domain was found in this sensitivity analysis, which indicated that an imputation effect may interfere with the meta-analysis results (Supplemental Table 4). To identify the source of heterogeneity across trials, a sensitivity analysis was performed by using the random-effects model and indicated no significant differences in treatment effect on the attention domain after individual removal of each included trial, except the last included trial (22). In detail, the treatment effect

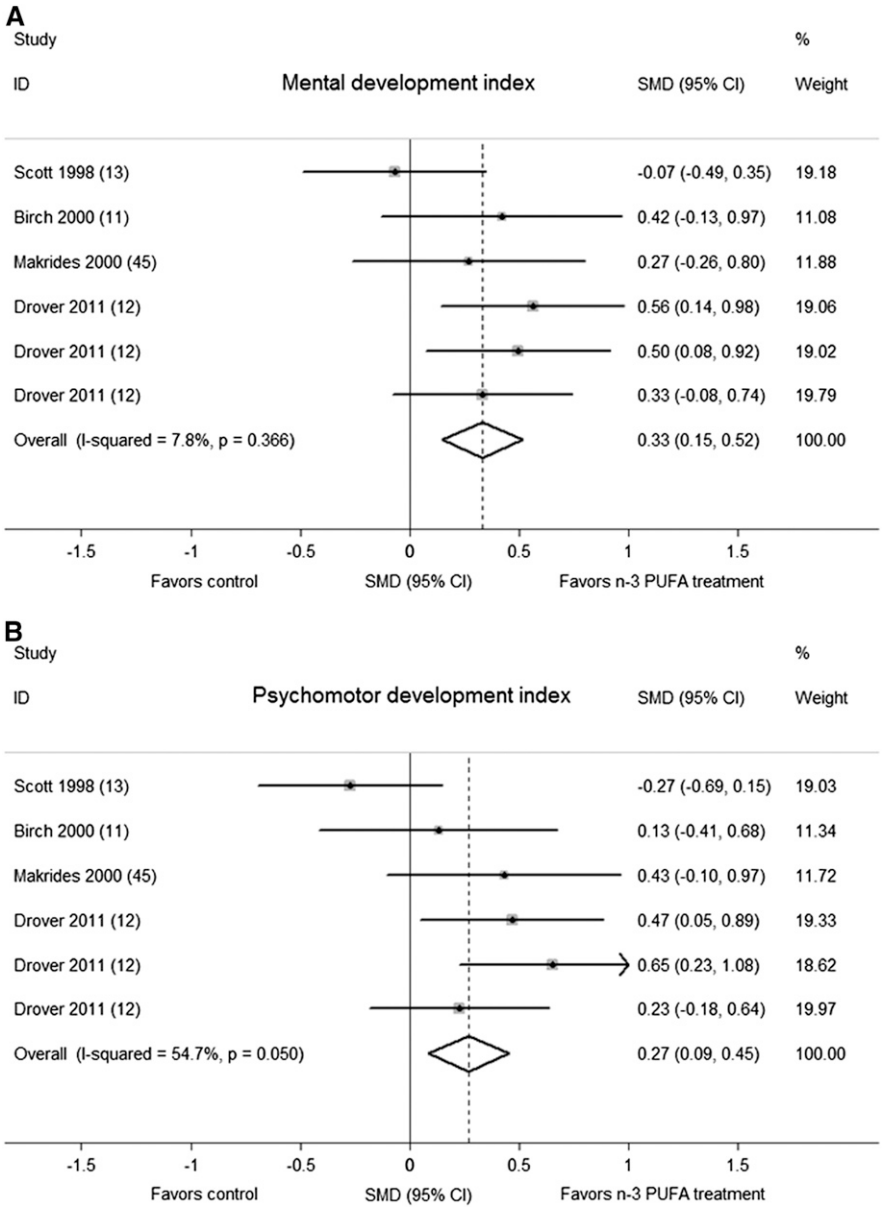

FIGURE 2 Treatment effects of n−3 PUFA supplementation on the Mental Development Index (A) and the Psychomotor Development Index (B) in infants during their cognitive development. The black dot data markers represent SMDs; the horizontal lines represent 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent the overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Drover trial (12) reported 3 dose levels in the n−3 PUFA treatment groups. ID, identification; SMD, standardized mean difference.

changed considerably (0.10; 95% CI: −0.03, 0.22), and the heterogeneity across trials for the attention domain was significantly reduced (I^2 = 2.5%, P = 0.392) after the removal of data from Lee et al. (22). (**Supplemental Table 6**). Furthermore, we tested for asymmetry using funnel plots to investigate small study effects and to visually identify possible bias (**Supplemental Figure 12**). However, the results of Egger's test showed that no significant small study effects for the attention domain (bias coefficient = 4.50; 95% CI: −0.43, 9.43; P = 0.064) were detected across these studies (**Supplemental Table 7**). In addition, we tested the treatment effects of MDI and PDI in infants, which showed a significant difference compared with controls. Finally, both the effects of MDI and PDI as estimated by sensitivity analysis and Egger's test showed little change and no small study bias, respectively. Details about the treatment effects of all primary outcomes as shown by Egger's test are shown in Supplemental Table 7.

Similarly, no significant heterogeneity was found in terms of treatment effect on the secondary outcomes, except for language, motor, and cognitive abilities in infants. To estimate the heterogeneity of treatment effects for these secondary outcomes, we visually inspected the asymmetry in funnel plots and found a possible small study bias for the treatment effects on language and cognitive abilities in a statistical view via the Egger's test (**Supplemental Figure 13** and **Supplemental Table 8**), which may be attributable to the publication of Birch et al. (11). This RCT reported fewer participants and a much more promising effect of n−3 PUFAs on the improvement of

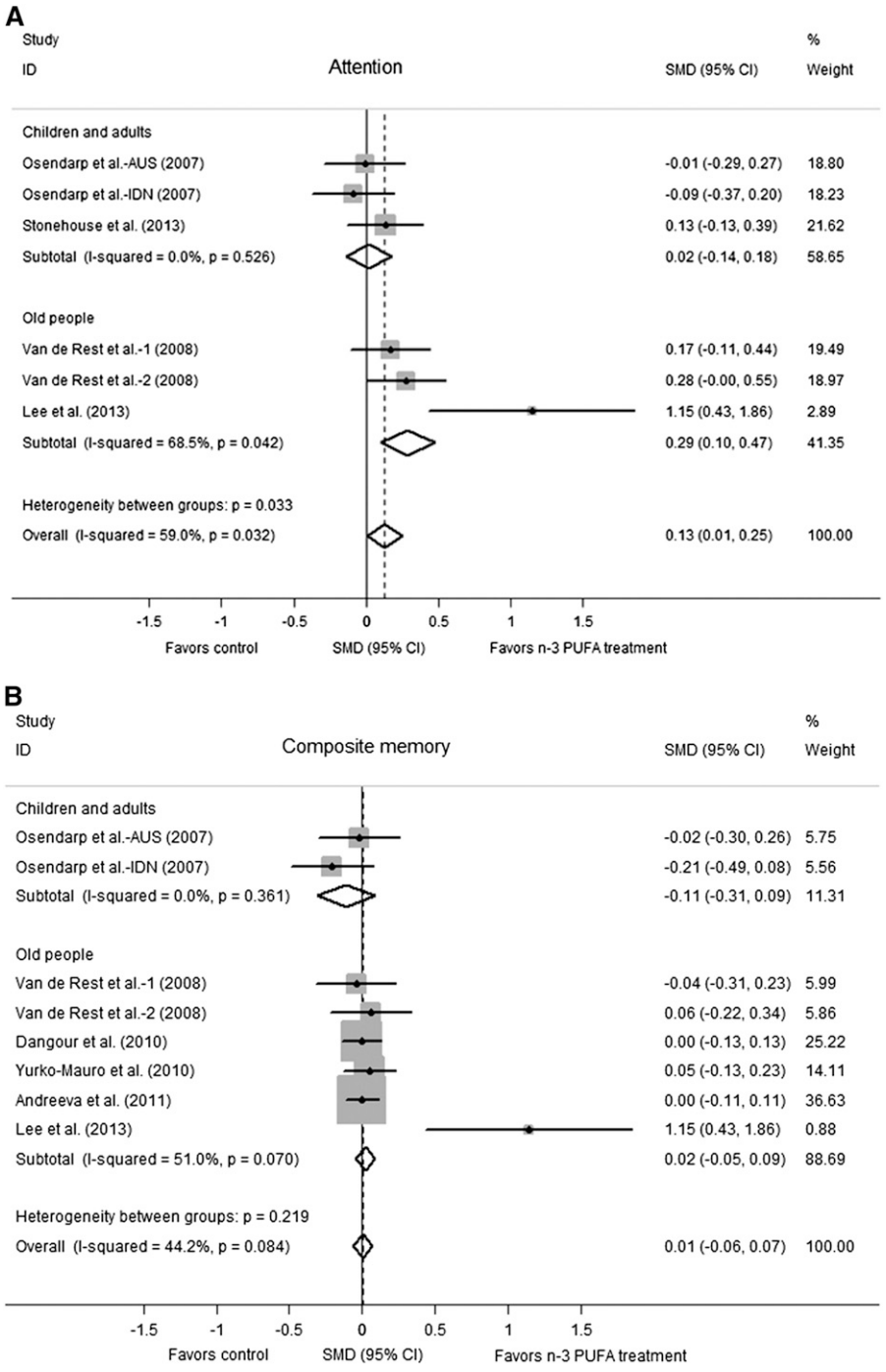

FIGURE 3 Treatment effects of n−3 PUFA supplementation on attention (A) and composite memory (B) of cognitive domains in children, adults, and the elderly. The black dot data markers represent SMDs; the horizontal lines represent the 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent each subgroup and overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Osendarp et al. and Van De Rest et al. trials (18, 20) reported 2 dose levels in the n−3 PUFA treatment groups. AUS, Australia; ID, indentification; IND, Indonesia; SMD, standardized mean difference.

cognitive development in infants than did the other included trials, which was probably regarded as the source of publication bias. However, such a bias could probably be excluded because the estimation of all treatment effects on language, motor, and cognitive abilities in the sensitivity analysis always showed positive results, with little change regardless of whether the publication of Birch et al. (11) was removed (**Supplemental Table 9**).

A meta-regression analysis was conducted to examine RCT characteristics such as treatment duration, n−3 PUFA dose, mean age, female ratio, and number of participants underlying the heterogeneity in all the investigated primary and secondary outcomes of cognitive function throughout the life span from infancy to old age. In detail, the regression models for investigating the association of every selected outcome with each of the above 5 RCT characteristics were established and

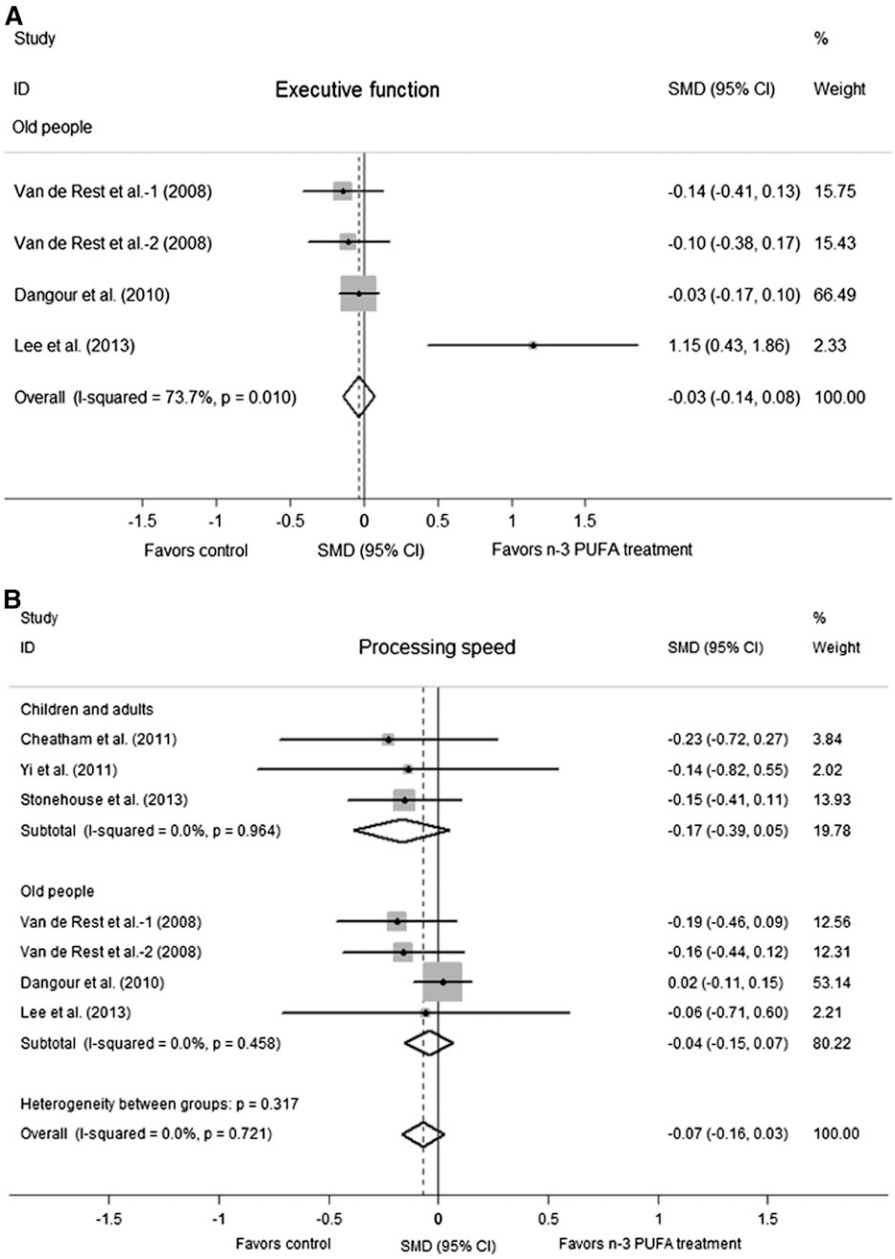

FIGURE 4 Treatment effects of n−3 PUFA supplementation on executive function (A) and processing speed (B) of cognitive domains in children, adults, and the elderly. The black dot data markers represent SMDs; the horizontal lines represent the 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent each subgroup and overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Van de Rest et al. trial (20) reported 2 dose levels in the n−3 PUFA treatment groups. ID, identification; SMD, standardized mean difference.

statistically evaluated. Our results indicated no associations between any of the treatment effects or outcomes with either of the above RCT characteristics (**Supplemental Table 10**).

DISCUSSION

Long-chain PUFAs (LCPUFAs) may be responsible for the potential gaps in cognitive development observed between breastfed and formula-fed infants. The n−3 LCPUFAs, especially EPA and DHA, play a crucial role in fetal development and infant growth (62). Previous studies have shown that infants who were fed formula deficient in LCPUFAs had significantly lower concentrations of EPA and DHA in plasma and red blood cells than did infants fed LCPUFA-supplemented formula (11, 63). We concluded that n−3 PUFA supplements, in the form of either capsules or formula, could benefit cognitive development in infants, based on promising improvements in MDI and PDI and significant promotion in language, motor, and cognitive abilities. Several RCTs have reported the effects of both EPA + DHA and arachidonic acid (an n−6 PUFA) on cognitive development but had controversial outcomes (64–68). Previous meta-analyses concluded that simultaneous n−3 and n−6 PUFA supplementation during pregnancy failed to show a significant effect on infant cognition or growth (8, 27). Nutritional evidence

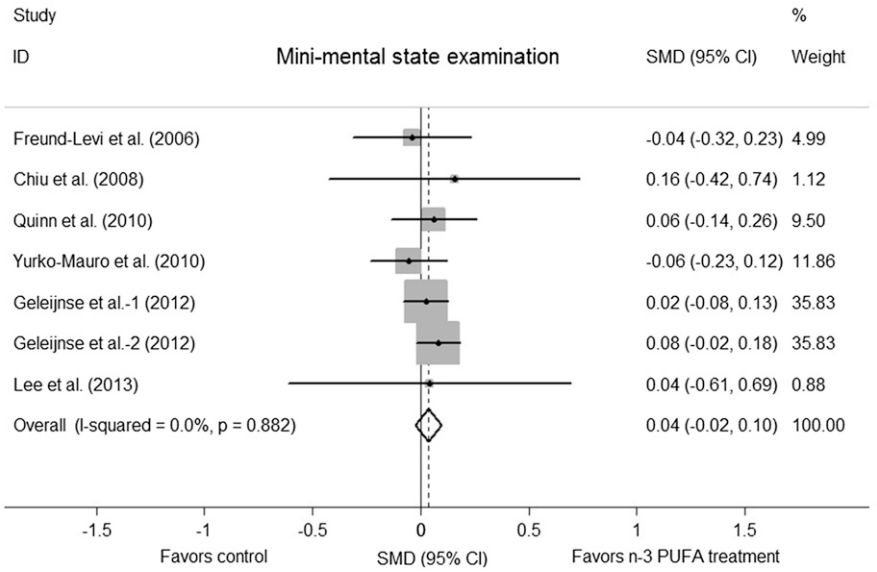

FIGURE 5 Treatment effects of n−3 PUFA supplementation on Mini-Mental State Examination results in the elderly. The black dot data markers represent SMDs; the horizontal lines represent the 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Geleijnse et al. trial (58) reported 2 dose levels in the n−3 PUFA treatment groups. ID, identification; SMD, standardized mean difference.

has shown that long-term n−3 PUFA deficiency reduces DHA concentrations and enhances n−6 PUFA concentrations, especially those of docosapentaenoic acid [22:5, n−6 (ω-6)] in brain (2, 6). Unfortunately, high concentrations of docosapentaenoic acid instead of DHA may have negative effects on cognitive development (6). Some included studies, such as that of Makrides et al. (9), reported that infants receiving DHA-only supplemented formula had higher MDI and PDI scores than did infants receiving DHA + arachidonic acid–supplemented formula (45). Furthermore, the inclusion of trials that used formulas providing close to the worldwide mean level of DHA in breast milk (0.32% DHA) was more likely to yield functional benefits attributable to DHA (69). The beneficial effects of DHA supplementation in infants were supported by several mechanistic investigations, which indicated that DHA supplementation can affect many specific processes and structures during development of the central nervous system. DHA is capable of influencing gene transcription and modifying the fluidity and thickness of neuronal membranes, thereby affecting receptor function, which is important for the developing brain and cognitive functionalities (2).

We found that n−3 PUFAs did not improve the memory, executive function, attention, and processing speed domains of human cognitive function after combining the results of imputation effect–related sensitivity analyses. Although most of the included studies used doses of DHA that exceeded the above recommendation, the results of the meta-regression indicated that the n−3 PUFA dose was not related to the treatment effect. Many of the included trials reported a statistically significant increase in plasma n−3 PUFA concentrations (15, 19, 32, 51, 60). However, the current meta-analysis showed no significant improvements in memory function in any of the selected outcomes. Previous meta-analyses of the cognitive benefits of n−3 PUFA supplementation in both cognitively impaired and intact subjects also concluded that there were no substantial beneficial effects in healthy subjects (26). Also, one important aspect of adult cognitive performance is the possible presence of underlying psychiatric disorders, such as attention-deficit disorders and depression, which may be present in children and adults and could affect cognitive performance. Furthermore, the possible mechanism relevant to the clinical cognitive benefits of n−3 PUFAs remains unclear, and the future mode of action elucidation would be informative. In terms of the attention domain in the current study, subgroup analyses showed significant improvements with n−3 PUFA treatment and observed differences in the Stroop effect—a secondary endpoint. Despite the acknowledged view that an age-related decrease in the efficiency of inhibitory processes accounted for age-related increases in the Stroop effect (70), a previous meta-analysis argued that Stroop interference effects possess apparent age-sensitivity (71). Although no association between the Stroop effect outcome and participant age was found in current meta-regression analysis ($\beta = -0.005$; 95% CI: −0.012, 0.002; $P = 0.111$), more clinical trials regarding the effect of n−3 PUFAs on the Stroop effect in age-dependent groups need to be conducted. Combined with the imputation effect–related sensitivity analysis and presence of confirmed heterogeneity source, the positive effect of n−3 PUFAs on the attention domain and on the Stroop effect (secondary endpoint) remains debatable.

On the basis of the analysis of MMSE and ADAS-Cog outcomes, our study indicated that n−3 PUFAs had no effect on cognitive decline or AD. The treatment effects of these outcomes were consistent across studies; neither heterogeneity nor small study bias were observed in any of the included studies. Animal studies have provided considerable evidence that n−3 PUFAs, especially DHA, are capable of protecting against cognitive decline, AD, and related neuropathological disorders (35, 72). In human studies, it might be valuable to conduct further clinical trials of long-term n−3 PUFA supplementation in patients with mild cognitive impairment and AD. To fully understand the benefits of n−3 PUFAs on cognitive function, other cognitive diseases—such as Huntington disease and

Parkinson disease—should be studied. Furthermore, possible interactions with apolipoprotein E4, antioxidants, environmental hazards, and dietary intake of n−6 PUFAs should be investigated further (35).

The strengths of the current study included the identification and systematic review of all RCTs that studied the effect of n−3 PUFA supplementation on cognition from the major medical literature databases. All 34 of the included clinical trials were RCTs and were identified by using a comprehensive search strategy, which included many terms and phrases related to *n−3 PUFA* and *cognition*. Moreover, we only included in the pooled analysis RCTs that had a treatment duration of ≥3 mo (or 12 wk) and used an n−3 PUFA supplement intervention with a certain daily n−3 PUFA ingredient intake. The current study investigated the benefits of n−3 PUFAs on human cognition throughout the whole life span and ultimately showed a substantial application of n−3 PUFAs for cognitive protection in infants but not in all people. Furthermore, the primary and secondary outcomes were considered in the meta-analysis only when data extraction and synthesis could be generated from ≥3 pooled studies with consolidated methods for outcome measures. In addition, we successfully identified possible sources of heterogeneity across the studies via the combined use of sensitivity and subgroup analyses, funnel plots, and Egger's test for the evaluation of small study bias and meta-regression.

The current study also had limitations regarding the design of the included trials, nonpooled cognitive outcomes, incomplete outcome measures, and geographic distribution of the populations. Using the Cochrane Risk of Bias Tool, several studies presented design concerns leading to potential bias from vague allocation concealment and blinding methods, which can negatively affect the identification of the benefits of n−3 PUFAs on cognitive function. Some other outcomes could not be pooled for the meta-analysis because of limited data reported in different trials and the lack of measurement criteria or baseline data. These outcomes included, but were not limited to, the following: *1*) behavior rating scale and intelligence quotient of infants; *2*) scores of strengths and difficulties questionnaire, scores of Kaufman Assessment Battery for Children, and word reading of children, adults, or the elderly; and *3*) the clinical dementia rating sum-of-boxes and the neuropsychiatric inventory of the elderly. Also, incompletely reported outcome measures resulted in fewer included studies than expected, which limited the power of the Q and I^2 statistic tests for the presence of heterogeneity in the current meta-analysis (73, 74). Finally, most of the trials included populations from developed countries, such as the United States, the United Kingdom, and Australia. Populations from Asia, Africa, and South America should be considered because economic conditions and the social burden of poverty may impede cognitive function (75). Overall, n−3 PUFA supplementation may provide some benefits on the selected domains of cognition in infants. The findings of the current study have considerable implications for clinical recommendations regarding cognition and mental health in age-specific populations. For instance, the n−3 PUFA ingredients in formula and related clinical nutritional observations for serving the infants should be considered. However, clinical trials on the intervention effect of n−3 PUFAs on cognitive behaviors in children and adults should be carefully evaluated before execution. Also, the high degree of heterogeneity for secondary outcomes among the included infant studies should be taken into consideration, although promising pooled analysis for these outcomes was reported.

In conclusion, in infants, n−3 PUFA supplementation could significantly benefit cognitive development based on comprehensive improvements in MDI and PDI and in language, motor, and cognitive abilities. However, n−3 PUFA supplementation was not associated with significant improvements in cognitive function in older children, adults, and the elderly and did not prevent cognitive decline or related neuropathological diseases in the elderly. Over the entire life span from infancy to old age, an appropriate intake of n−3 PUFA supplements is recommended during infancy. However, such supplements do not appear to benefit cognitive performance during the remaining life span. To improve the quality of RCTs for future perspectives, the presentation of details about adequate randomization and blinding methods is strongly recommended. In addition, incomplete outcome data and selective reporting should be avoided as much as possible so that more eligible and high-quality RCTs can be included in meta-analyses. Finally, it would be of interest to investigate the effects of n−3 PUFA–rich diets—such as a fish-heavy diet and a Mediterranean diet—on cognitive function.

The authors' responsibilities were as follows—JJ, QL, and SZ: designed the research; JJ and QL: conducted the library search and wrote the manuscript; JJ, QL, and JC: extracted and controlled the data and assumed primary responsibility for the final content; JJ, QL, JC, WZ, and MY: controlled and analyzed the data; and JJ and SZ: contributed to the writing of the manuscript. All of the authors read and approved the final manuscript. None of the authors, or their close relatives, has a financial interest in or serves as an employee, officer, member, owner, trustee, or agent for an organization that has a financial interest in the outcome of this study. JJ received funding for the submitted work from the National Natural Science Foundation of China and Zhejiang Provincial Natural Science Foundation of China, which have no financial interest in the outcome of this study. The funders had no role in the study design, implementation, analysis, or interpretation of the data.

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Original Investigation

Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function
The AREDS2 Randomized Clinical Trial

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IMPORTANCE Observational data have suggested that high dietary intake of saturated fat and low intake of vegetables may be associated with increased risk of Alzheimer disease.

OBJECTIVE To test the effects of oral supplementation with nutrients on cognitive function.

DESIGN, SETTING, AND PARTICIPANTS In a double-masked randomized clinical trial (the Age-Related Eye Disease Study 2 [AREDS2]), retinal specialists in 82 US academic and community medical centers enrolled and observed participants who were at risk for developing late age-related macular degeneration (AMD) from October 2006 to December 2012. In addition to annual eye examinations, several validated cognitive function tests were administered via telephone by trained personnel at baseline and every 2 years during the 5-year study.

INTERVENTIONS Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo were tested in a factorial design. All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc.

MAIN OUTCOMES AND MEASURES The main outcome was the yearly change in composite scores determined from a battery of cognitive function tests from baseline. The analyses, which were adjusted for baseline age, sex, race, history of hypertension, education, cognitive score, and depression score, evaluated the differences in the composite score between the treated vs untreated groups. The composite score provided an overall score for the battery, ranging from −22 to 17, with higher scores representing better function.

RESULTS A total of 89% (3741/4203) of AREDS2 participants consented to the ancillary cognitive function study and 93.6% (3501/3741) underwent cognitive function testing. The mean (SD) age of the participants was 72.7 (7.7) years and 57.5% were women. There were no statistically significant differences in change of scores for participants randomized to receive supplements vs those who were not. The yearly change in the composite cognitive function score was −0.19 (99% CI, −0.25 to −0.13) for participants randomized to receive LCPUFAs vs −0.18 (99% CI, −0.24 to −0.12) for those randomized to no LCPUFAs (difference in yearly change, −0.03 [99% CI, −0.20 to 0.13]; $P = .63$). Similarly, the yearly change in the composite cognitive function score was −0.18 (99% CI, −0.24 to −0.11) for participants randomized to receive lutein/zeaxanthin vs −0.19 (99% CI, −0.25 to −0.13) for those randomized to not receive lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, −0.14 to 0.19]; $P = .66$). Analyses were also conducted to assess for potential interactions between LCPUFAs and lutein/zeaxanthin and none were found to be significant.

CONCLUSIONS AND RELEVANCE Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.

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Editorial page 774

Related article page 781

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The prevalence of Alzheimer disease, estimated to have affected 5.2 million people in the United States in 2013, may triple in the next 4 decades.[1] Epidemiologic studies have suggested that diets high in omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) have a protective role in maintaining cognitive function.[2] Docosahexaenoic acid (DHA), a component of omega-3 LCPUFA, is an essential structural component of the brain cells, and low levels of DHA have also been found in persons with Alzheimer disease.[3] For these reasons, omega-3 LCPUFAs were tested for the treatment of dementia. However, numerous randomized clinical trials (RCTs) failed to show omega-3 LCPUFAs to be effective in treating dementia.[4,5]

Similarly, observational data suggested that high dietary intake or high plasma levels of antioxidants may also be associated with better cognitive performance,[6-8] but RCTs did not support this hypothesis.[9,10] Results of an RCT of beta carotene suggested that this carotenoid might be important in the treatment of dementia, depending on the duration of supplementation.[11] A possible role for lutein and zeaxanthin in the treatment of cognitive impairment in older adults has also been raised in a small RCT of lutein combined with omega-3 LCPUFAs in 49 women with limited follow-up.[12]

The Age-Related Eye Disease Study 2 (AREDS2),[13] an RCT[14] of omega-3 fatty acids and/or lutein/zeaxanthin supplements for the treatment of age-related macular degeneration (AMD) and cataract, provided an opportunity to evaluate the role of these oral supplements in preventing cognitive decline. AREDS2 enrolled one of the largest numbers of study participants for cognitive function testing at baseline and every 2 years, in a study with long-term follow-up periods (median of 5 years), providing a more definitive result showing the effects of oral nutritional supplementation on cognition.

Methods

The study design is reported in Supplement 1.[13] AREDS2 limited enrollment to people at high risk of progressing to late AMD, those with either bilateral large drusen, or large drusen in one eye and late AMD in the fellow eye. The clinical research was conducted according to the Declaration of Helsinki and all institutional review boards approved the AREDS2 research protocol. All participants provided written informed consent for AREDS2. At the time of randomization, study participants were asked whether they agreed to be contacted for the ancillary study. Within 3 months following randomization, verbal informed consent was obtained and written materials regarding the AREDS2 Cognitive Function Study were provided to the study participants.

This study, supported by the National Institutes of Health (NIH), was required to gather information on race and ethnicity. Using guidelines from the *NIH Health Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research*, self-reported race and ethnicity of the AREDS2 participants were collected with 2 ethnic categories (Hispanic or Latino and not Hispanic or Latino) and 5 racial categories (American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other Pacific Islander, and white). Participants were able to select more than 1 racial category.

AREDS2 was a randomized, double-masked, placebo-controlled, 2 × 2 factorial trial evaluating the risks and benefits of adding omega-3 LCPUFAs (specifically docosahexaenoic acid [DHA], 350 mg, and eicosapentaenoic acid [EPA], 650 mg, and/or lutein/zeaxanthin, 10 mg/2 mg) to the original AREDS formulation, or one of the variations of the AREDS formulation for the treatment of AMD. Study participants were randomly assigned in a 1:1:1:1 allocation to take one of the following study supplements daily: (1) placebo; (2) DHA/EPA; (3) lutein/zeaxanthin; or (4) DHA/EPA and lutein/zeaxanthin. The investigational products matched the placebos in size, shape, and taste. The original randomization scheme is displayed in eFigure 1 in Supplement 2.[15]

Because they are known to be at high risk for developing late AMD, all AREDS2 participants were also offered the original or a modified version of the AREDS formulation. A second randomization was conducted to evaluate the effect of eliminating beta carotene from the AREDS supplements (beta carotene vs no beta carotene) and the effect of comparing 80 mg of zinc vs 25 mg of zinc. Participants who consented to the optional secondary randomization were randomly assigned to receive: (1) AREDS formulation (vitamins C, 500 mg; E, 400 IU; beta carotene, 15 mg; zinc oxide, 80 mg; and cupric oxide, 2 mg); (2) AREDS formulation minus beta carotene; (3) AREDS formulation with low zinc (25 mg); or (4) AREDS formulation minus beta carotene and low zinc. Current smokers and former smokers who had quit within 1 year before randomization and who agreed to this secondary randomization were randomized to 1 of the 2 groups without beta carotene because beta carotene supplementation has been shown to increase the risk of lung cancers in cigarette smokers.[16,17] Participants who did not consent to this secondary randomization were provided with the original AREDS supplements if they were not current smokers or had not smoked within the past year. The flow diagram for the secondary randomization is available in a previously published report.[15]

The primary and secondary randomizations were stratified by clinical center and AMD category (bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye) using randomly permuted blocks of varying sizes. Each treatment was assigned 5 bottle numbers. Bottle numbers were issued via an electronic randomization system for each participant once study eligibility was verified. The assigned bottle number was used to distribute the study treatment(s). AREDS2 Coordinating center personnel involved in creating the randomization system had access to the bottle number/treatment assignments. Participants and study personnel were masked to treatment assignment. Participants received their study supplements or matching placebos at each annual visit. Adherence with the study supple-

ments was measured with annual pill counts. In a subset of participants, the serum levels were also evaluated for adherence at baseline and years 1, 3, and 5. Follow-up study visits were scheduled annually with telephone contacts by study coordinators at 6 months between study visits and at 3 months postrandomization to collect information on AMD treatment and adverse events. Investigators, also masked to all medical data and treatment assignments, conducted the analyses.

Cognitive Function Tests

AREDS2 used a cognitive battery similar to the one used in AREDS, administered by certified personnel by telephone over a period of 30 minutes (eMethods in Supplement 2).[9] The cognitive function test administrators, who were masked to the participant's study supplement assignment and medical history, received extensive initial training as well as certification on interview techniques and scoring of responses. Subsequently, quarterly reviews of 3 randomly selected interviews on audiotape from each interviewer were centrally conducted to provide feedback regarding the interview and scoring techniques for quality assurance. The first administration of the AREDS2 telephone battery instruments was within 3 months after randomization to the primary AREDS2 protocol and approximately every 2 years thereafter.

The AREDS Telephone Battery was originally found to be an appropriate substitute for participants who were unable to complete an in-clinic assessment of cognitive function.[18] All tests have been validated and used in previous studies with cognitive function testing. An abbreviated version of the cognitive battery consisting of the Hearing Handicap Inventory, CES-D (Center for Epidemiologic Studies' Depression Scale), and TICS (Telephone Interview of Cognitive Status) (all of which took approximately 10-15 minutes to administer) was administered to participants who had time constraints or other concerns about undergoing the full-length battery. The AREDS2 cognitive battery consisted of 8 tests of cognitive function that were administered after each participant was tested for hearing and depression at each telephone call for cognitive function testing. The order of testing is listed in the Box. The ranges of the values for these individual tests are described in eAppendix in Supplement 2.

Box. AREDS2 Cognitive Battery Tests by Order of Administration[a]

1. The Hearing Handicap Inventory[19] is given first because the interview is conducted by telephone
2. The Center for Epidemiologic Studies' Depression Scale (CES-D)[20] is designed to assess symptoms of depression in the general population
3. The Telephone Interview Cognitive Status-Modified (TICS-M)[21] is a version of the Mini Mental State Examination; TICS-M also includes 10 words that are given early and tested for immediate and delayed recall
4. The Animal Category[22] is used, together with the tests of letter fluency and alternating fluency (items 5 and 6), to assess language and executive function; participants are asked to name as many animals as possible within 1 minute
5. Letter Fluency[22] is used with animal and alternating fluency; participants are asked to name as many words starting with the letters *F*, *A*, and *S* as possible within 1 minute
6. Alternating Fluency[22] is used with animal and letter fluency; participants are instructed to alternately name a word beginning with the letter *C* and a food category in 1 minute
7. The Wechsler Memory Scale, Third Edition (WMS-III), Logical Memory Part I and Part II[23] measures both immediate and delayed recall of 2 stories, the test assesses 2 domains of cognitive function: attention and memory
8. Digits Backward[24] is a task used to test the speed of processing task, in which the participant is asked to count as fast as they can backward starting from 100 for 30 seconds
9. Delayed recall of the WMS-III Recall paragraph
10. TICS-M Recall consisted of recalling the 10 words initially read with the TICS

[a] Only test items 3 through 10 were used for scoring.

Outcome Measurements

The primary outcome in the planned ancillary study of cognition evaluated the yearly change in the composite scores of the cognitive function tests (items 3-10 in the Box). A higher change in score indicated better cognition vs negative values, which represented worsening of the cognitive function testing. We assessed the difference in the yearly change of the scores by treatment main effects, focused mainly on omega-3 LCPUFAs vs no omega-3 LCPUFAs, as stated a priori. Secondary analyses included lutein/zeaxanthin vs no lutein/zeaxanthin, high zinc vs low zinc, and beta carotene vs no beta carotene, because these nutrients were previously explored in other studies. However, this ancillary study was not sufficiently powered to evaluate these additional nutrients.

The change in the TICS total score, a comprehensive testing of all the domains over the course of the study from baseline, was assessed.[25] A composite score was constructed by converting the test results of the 8 cognitive tests (Box) *z* scores and then adding the *z* scores. The composite score provided an overall score for the battery, ranging from −22 to 17, with higher scores representing better function.[18] This methodology has been used in previously published studies of cognitive function testing.[26,27] We also individually evaluated the yearly change in the cognitive function scores for the 8 cognitive function tests from baseline to 2 and 4 years. Composite scores were analyzed only in those participants who completed the entire battery of cognitive function tests, while those who had a TICS score only were analyzed for all participants who had TICS scores available in the entire cohort.

Statistical Analyses

The primary hypothesis, stated at the beginning of the AREDS2 ancillary cognitive function study, was to test whether omega-3 LCPUFAs (the main effects of those who

were randomized to receive omega-3 LCPUFAs vs those not randomized to receive omega-3 LCPUFAs) would have any effect on cognitive function. It was estimated that 15% to 35% of the AREDS2 participants would have a score greater than the normal range for the TICS. We assumed that at least 3000 AREDS2 participants (1500 assigned to receive omega-3 LCPUFAs and 1500 assigned to receive no omega-3 LCPUFAs) would have at least 85% power to detect an odds ratio (OR) of 0.75, as measured by the TICS, assuming a 2-sided $\alpha = .05$ and a control group (no omega-3 fatty acids) rate of participants with a score greater than the normal range. The study was powered to evaluate only the main effects of omega-3 LCPUFAs, but because this is a factorial design, studies of interaction were also conducted to assess for potential interactions between omega-3 LCPUFAs and lutein/zeaxanthin.

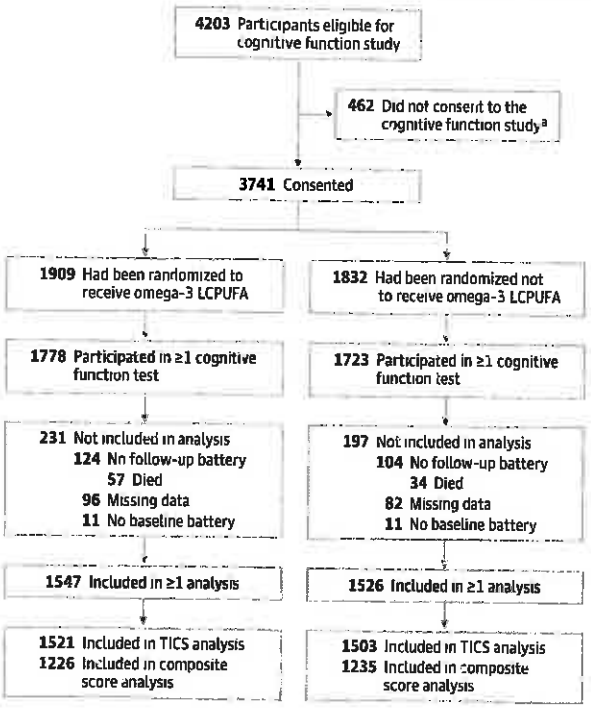
For each test of cognitive function, changes in score from baseline to time of study visits at 2 and 4 years were evaluated using a mixed-model regression. The models took into account the repeated measures of the participants, the unequal time spacing, and number of cognitive tests for each participant by using a spatial power covariance structure. The models provided estimates of yearly change in score that could be associated with the AREDS2 study supplement assignment and each covariate. The models were adjusted for baseline age, sex, race, history of hypertension, education, baseline cognitive score, and baseline depression score. Age, baseline score, and baseline depression score were treated as continuous variables, and the others were treated as categorical variables with race dichotomized to white vs nonwhite. A repeated-measures logistic regression was used to analyze the outcome of a TICS score of less than 30. To account for the correlation of multiple visits per participant, an autoregressive correlation structure was used. To account for multiplicity of analyses, we used 99% CIs rather than the conventional 95% CI. Because 36 models were conducted, to be statistically significant, the *P* value would need to be <.001.

Participants were excluded from the analyses if they were missing baseline cognitive function tests, any follow-up test, an incomplete test, or missing baseline demographic data. All analyses were conducted under the principle of intention to treat and no data imputation was applied. All analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Results

A total of 4203 participants were enrolled between October 2006 and September 2008 at 82 clinical sites across the United States and followed up until December 2012 in AREDS2. Enrollees had to satisfy the specified inclusion and exclusion criteria.[13] Of the 4203 AREDS2 participants enrolled, 3741 (89%) consented to the full Cognitive Function Study, 462 declined, and 3501/3741 (93.6%) underwent cognitive function testing (**Figure 1**). Of the 3501 who consented, 2991 (85%) participated in this study by completing

Figure 1. Flow of AREDS2 Participants



Flow diagram shows the AREDS2 participants included in the analyses of the ancillary cognitive function study. LCPUFAs indicate long-chain polyunsaturated fatty acids; TICS, Telephone Interview of Cognitive Status.

[a] Reasons for declining consent were not collected.

at least 1 full interview and 510 (15%) had the shortened battery (eTable 1 in Supplement 2). Among those who consented for the present study, we excluded individuals with no baseline test, no follow-up test, or missing demographic data or incomplete tests, leaving us with 3073 participants for analyses. Of the 3 possible interviews for cognitive function during the course of the study (baseline, year 2, and year 4), 2831 of 3501 (81%) of study participants contributed to all 3 interviews, 410 (12%) had 2 interviews, and 260 (7%) had 1 interview only (eTable 1 in Supplement 2). The mean (SD) age of the participants in the Cognitive Function Study was 72.7 (7.7) years and 57.5% were women.

AREDS2 participants included in the analyses of the Cognitive Function Study were younger, more likely to be white, and more likely to have a higher level of education (eTable 2 in Supplement 2). Among those who participated, there was a fairly comparable distribution of the treatment assignments. However, among those who did not participate, there was a relatively greater proportion assigned to lutein/zeaxanthin (eTable 2 in Supplement 2). Baseline serum levels of the nutrients evaluated were comparable across treatment groups. **Table 1** describes the comparable baseline characteristics of the participants who were randomly assigned to receive omega-3 LCPUFAs (DHA/EPA) or no omega-3 LCPUFAs (DHA/EPA).

Table 1. Baseline Characteristics of AREDS2 Participants in at Least 1 Analysis by Assignment to Omega-3 LCPUFAs

Baseline Characteristic	No. (%)		
	No LCPUFAs (n = 1526)	LCPUFAs (n = 1547)	*P* Value[a]
Age, mean (SD), y	72.7 (7.8)	72.7 (7.7)	.88
Women	858 (56.2)	909 (58.8)	.16
Race			
White	1485 (97.3)	1501 (97.0)	
Black	14 (0.9)	21 (1.4)	
Asian	9 (0.6)	9 (0.6)	
American Indian	2 (0.1)	3 (0.2)	.85
Native Hawaiian or other Pacific Islander	2 (0.1)	1 (0.1)	
Other	14 (0.9)	12 (0.8)	
Education			
≤High school	442 (29.0)	456 (29.5)	
≥Some college	720 (47.2)	773 (50.0)	.08
Postgraduate	364 (23.9)	318 (20.6)	
Smoking status			
Never	649 (42.5)	664 (42.9)	
Former	769 (50.4)	789 (51.0)	.53
Current	108 (7.1)	94 (6.1)	
CES-D, mean (SD), score[b]	15.7 (6.3)	16.1 (6.6)	.08
Aspirin use	740 (48.5)	762 (49.3)	.67
Statin use	686 (45.0)	672 (43.4)	.40
Medical history			
Hypertension	872 (57.1)	902 (58.3)	.51
Congestive heart failure	57 (3.7)	51 (3.3)	.51
Coronary heart disease	154 (10.1)	130 (8.4)	.11
Myocardial infarction	106 (6.9)	84 (5.4)	.08
Stroke	74 (4.8)	78 (5.0)	.80

Abbreviations: AREDS2, Age-Related Eye Disease Study 2; CES-D, Center for Epidemiologic Studies' Depression Scale; LCPUFAs, long-chain polyunsaturated fatty acids.

[a] *P* values were calculated using χ^2 tests for categorical variables and *t* tests for numeric variables.

[b] The CES-D cutoff score of 16 (or greater) indicates individuals at risk for clinical depression.

Table 2. Cognitive Function Test Scores at Baseline by Assignment to Omega-3 LCPUFAs

Cognitive Function Test	No LCPUFAs	LCPUFAs	Difference, Mean (99% CI)	*P* Value[a]
Composite score[b]				
No. of participants	1235	1226		
Z score, mean (SD)	0.4 (5.4)	0.3 (5.2)	−0.19 (−0.73 to 0.36)	.38
TICS score[c]				
No. of participants	1503	1521		
Points, mean (SD)	33.0 (3.4)	33.0 (3.4)	−0.04 (−0.35 to 0.27)	.75

Abbreviation: LCPUFAs, long-chain polyunsaturated fatty acids.

[a] *P* values were calculated using analysis of covariance comparing the means.

[b] The composite score was constructed by including the score of all 8 cognitive tests, converting all test results into *z* scores, then adding the *z* scores. The composite score was computed to obtain an overall score for the battery of cognitive function tests, which ranged from −22 to 17, with higher scores indicating better function.

[c] The Telephone Interview of Cognitive Status (TICS-M)[3] is a version of the Mini-Mental State Examination (score range, 0-39 points, with higher scores indicating better cognitive function).

Adherence to Study Medication and Loss to Follow-up Rate

Evaluation of adherence with the primary study supplements showed that 1439 of 1736 participants (82.9%) assigned to receive omega-3 LCPUFAs and 1419 of 1688 who were (84.1%) assigned to receive no omega-3 LCPUFAs were adherent to their study drugs at least 75% of the time and taking 75% or more of their study drugs. Similarly, 1432 of 1690 participants (84.7%) assigned to receive lutein/zeaxanthin and 1494 of 1724 (86.7%) who were assigned to not receive lutein/zeaxanthin took 75% or more of the study medications at least 75% of the time. In addition, serum levels of 545 AREDS2 participants who were randomized to the

Table 3. Telephone Interview of Cognitive Status and the Composite Scores by Baseline Characteristic

Characteristic	TICS Score, Mean (SD)[a] (n = 3024)	*P* Value[b]	Composite Score, Mean (SD)[c] (n = 2461)	*P* Value[b]
Age, y				
Tertile 1, 50-70	34.0 (3.1)		2.3 (5.0)	
Tertile 2, 71-78	33.0 (3.4)	<.001	0.1 (5.0)	<.001
Tertile 3, ≥79	31.9 (3.3)		−1.8 (5.1)	
Sex				
Women	33.4 (3.3)	<.001	0.9 (5.1)	<.001
Men	32.5 (3.3)		−0.4 (5.4)	
Race				
White	33.1 (3.3)		0.4 (5.2)	
Black	31.0 (3.4)		−2.1 (5.2)	
Asian	31.8 (3.9)		−1.2 (5.5)	
American Indian	28.8 (6.0)	<.001	−4.5 (8.2)	.002
Native Hawaiian or other Pacific Islander	29.3 (3.1)		−10.3[d]	
Other	30.0 (3.6)		−2.0 (5.1)	
Education				
≤High school	31.7 (3.5)		−2.4 (5.0)	
≥Some college	33.4 (3.1)	<.001	0.7 (4.9)	<.001
Post graduate	34.0 (3.0)		2.9 (4.9)	
Smoking status				
Never	33.2 (3.3)		0.5 (5.2)	
Former	32.9 (3.4)	.01	0.3 (5.3)	.45
Current	32.6 (3.5)		0.0 (5.7)	
Aspirin use				
No	33.1 (3.4)	.20	0.5 (5.4)	.21
Yes	32.9 (3.3)		0.2 (5.1)	
Statin use				
No	33.3 (3.3)	<.001	0.7 (5.3)	<.001
Yes	32.7 (3.4)		−0.1 (5.2)	
CES-D score ≥16[e]				
No	33.2 (3.3)	<.001	0.7 (5.2)	<.001
Yes	32.7 (3.4)		−0.2 (5.3)	
Medical history				
Hypertension				
No	33.4 (3.2)	<.001	0.9 (5.3)	<.001
Yes	32.8 (3.5)		−0.1 (5.2)	
Congestive heart failure				
No	33.1 (3.3)	<.001	0.4 (5.2)	<.001
Yes	31.3 (3.8)		−1.6 (5.2)	
Coronary heart disease				
No	33.2 (3.3)	<.001	0.6 (5.2)	<.001
Yes	31.7 (3.4)		−2.3 (4.8)	
Myocardial infarction				
No	33.1 (3.3)	<.001	0.5 (5.2)	<.001
Yes	31.6 (3.9)		−1.9 (5.6)	
Stroke				
No	33.1 (3.3)	<.001	0.5 (5.2)	<.001
Yes	31.8 (3.7)		−1.7 (5.5)	

Abbreviation: CES-D, Center for Epidemiologic Studies' Depression Scale.

[a] The Telephone Interview of Cognitive Status (TICS-M)[3] is a version of the Mini-Mental State Examination (score range, 0-39 points, with higher scores indicating better cognitive function).

[b] *P* values were calculated by using an analysis of covariance comparing the means.

[c] The composite score was constructed by including the score of all 8 cognitive tests, converting all test results into *z* scores, then adding the *z* scores. The composite score was computed to obtain an overall score for the battery of cognitive function tests, which ranged from −22 to 17, with higher scores indicating better function.

[d] N = 1.

[e] The CES-D cutoff score of 16 (or greater) indicates individuals at risk for clinical depression.

Table 4. Association of Risk Factors With Score Change in the Telephone Interview of Cognitive Status and the Composite Score

Characteristic	TICS[b] Score Change/y (99% CI)[a]	TICS[b] P Value	Composite Score[c] Score Change/y (99% CI)[a]	Composite Score[c] P Value
Age, per year	−0.05 (−0.06 to −0.05)	<.001	−0.05 (−0.07 to −0.04)	<.001
Years from baseline, per year	−0.11 (−0.15 to −0.07)	<.001	−0.18 (−0.23 to −0.14)	<.001
Score at baseline test, 1-point increment	−0.24 (−0.26 to −0.22)	<.001	−0.09 (−0.11 to −0.08)	<.001
CES-D[c] score at baseline, 1-point increment	−0.01 (−0.02 to 0.00)	.004	−0.01 (−0.02 to 0.00)	.05
Men (vs women)	−0.30 (−0.45 to −0.16)	<.001	−0.33 (−0.50 to −0.16)	<.001
White race (vs nonwhite)	0.53 (0.10 to 0.97)	.002	0.51 (−0.04 to 1.05)	.02
Education				
≥Some college	0.43 (0.25 to 0.60)		0.30 (0.10 to 0.51)	
Postgraduate	0.77 (0.56 to 0.98)	<.001	0.50 (0.25 to 0.75)	<.001
≤High school	1 [Reference]		1 [Reference]	
History of hypertension	−0.12 (−0.27 to 0.02)	.03	−0.13 (−0.30 to 0.04)	.05

Abbreviation: CES-D, Center for Epidemiologic Studies' Depression Scale.

[a] Estimated score change per year (99% CIs) were calculated using 2 separate mixed-models regression.

[b] The Telephone Interview of Cognitive Status (TICS-M)[3] is a version of the Mini-Mental State Examination (score range, 0-39 points, with higher scores indicating better cognitive function).

[c] The composite score was constructed by including the score of all 8 cognitive tests, converting all test results into z scores, then adding the z scores. The composite score was computed to obtain an overall score for the battery of cognitive function tests, which ranged from −22 to 17, with higher scores indicating better function.

treatments showed a 2-fold or greater increase in the serum levels of omega-3 LCPUFAs and/or lutein/zeaxanthin, compared with those participants who were not assigned to receive the respective nutrients.

Cognitive Function Testing Scores

The baseline cognitive function scores for all the participants included in the various analyses are displayed in eTable 3 (in Supplement 2). The baseline scores from the cognitive function tests were comparable across the randomized groups of the main effects of omega-3 LCPUFAs vs no omega-3 LCPUFAs (Table 2). Similar balanced distribution was seen across all the randomized groups of all the other nutrients evaluated (eTable 4 in Supplement 2).

Overall Effects of the Nutrient Supplementation on Cognitive Function

Table 3 reports the baseline demographics and risk factors for the participants included in the TICS scores analyses and/or the composite scores analyses. Higher cognitive function scores indicate better cognition. For the outcome of the change at years 2 and 4 from baseline, calculated as yearly change, negative values signal a decrease in cognitive function when compared with baseline (Table 4). In general, the cognitive function testing scores decreased over time for the AREDS2 participants.

AREDS2 participants who achieved higher scores at baseline on both the TICS and the composite score were more likely to be women and white. Participants with higher levels of education also achieved higher scores on testing. Persons without a history of hypertension, congestive heart failure, coronary heart disease, myocardial infarction, and stroke were more likely to score higher in both TICS and composite scores.

Main Effects of Omega-3 LCPUFAs

The yearly change in the composite cognitive function score was −0.19 (99% CI, −0.25 to −0.13) for participants randomized to receive LCPUFAs and −0.18 (99% CI, −0.24 to −0.12) for those randomized to receive no LCPUFAs (difference in yearly change, −0.03 [99% CI, −0.20 to 0.13]; P = .63; Figure 2A). The difference in the yearly change of the TICS between the omega-3 LCPUFA treatment groups was −0.10 (99% CI, −0.24 to 0.04; P = .07; Figure 2A). Further evaluation of the TICS score for the odds of having a score less than 30 was conducted using a binary outcome of TICS score of less than 30, which is considered to be less than normal. The odds of having a TICS score of less than 30 was 1.12 (99% CI, 0.91 to 1.39; P = .15; Figure 3). The yearly changes of the various tests that contributed to the composite scores ranged from −0.10 to 0.17; none of these changes were statistically significant (Figure 2A).

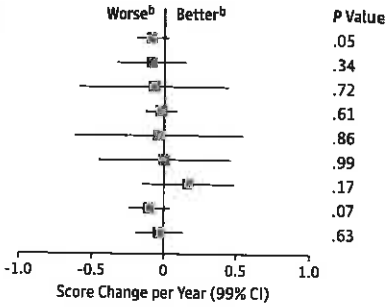
Main Effects of Lutein and Zeaxanthin

The yearly change in the composite cognitive function score was −0.18 (99% CI, −0.24 to −0.11) for participants randomized to receive lutein/zeaxanthin vs −0.19 (99% CI, −0.25 to −0.13) for those randomized to not receive lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, −0.14 to 0.19]; P = .66; Figure 2B). Similarly, the difference in the yearly TICS score change between the lutein/zeaxanthin treatment groups was −0.01 (99% CI, −0.16 to 0.13; P = .80; Figure 2B), and the odds of having TICS score of less than 30 was 1.08 (99% CI, 0.87 to 1.33; P = .35; Figure 3). The results of the tests

Figure 2. Results of the Mixed-Models Regression for the Change Per Year in Cognitive Function Test Scores From Baseline for Each of the Nutrients Tested

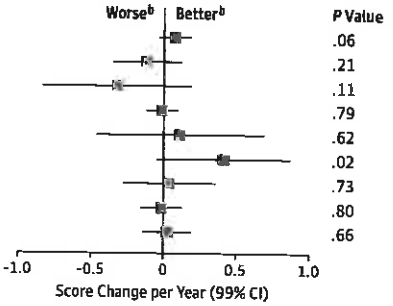
Omega-3 LCPUFA vs No Omega-3 LCPUFA[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	P Value
TICS word list recall[20]	2674	-0.08 (-0.19 to 0.03)	.05
Verbal fluency, animal[21]	2679	-0.09 (-0.33 to 0.15)	.34
Verbal fluency, letter[21]	2676	-0.07 (-0.59 to 0.44)	.72
Verbal fluency, alternating[21]	2665	-0.02 (-0.13 to 0.08)	.61
Wechsler logical memory I[22]	2682	-0.04 (-0.61 to 0.54)	.86
Wechsler logical memory II[22]	2675	0.00 (-0.46 to 0.46)	.99
Backwards counting[23]	2678	0.17 (-0.15 to 0.49)	.17
TICS total[c]	3063	-0.10 (-0.24 to 0.04)	.07
Composite score[d]	2636	-0.03 (-0.20 to 0.13)	.63



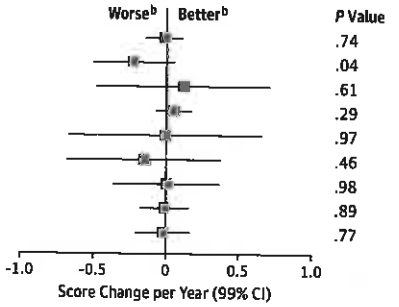
Lutein/Zeaxanthin vs No Lutein/Zeaxanthin[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	P Value
TICS word list recall[20]	2674	0.08 (-0.03 to 0.19)	.06
Verbal fluency, animal[21]	2679	-0.12 (-0.35 to 0.12)	.21
Verbal fluency, letter[21]	2676	-0.32 (-0.84 to 0.19)	.11
Verbal fluency, alternating[21]	2665	-0.01 (-0.12 to 0.09)	.79
Wechsler logical memory I[22]	2682	0.11 (-0.46 to 0.69)	.62
Wechsler logical memory II[22]	2675	0.41 (-0.05 to 0.87)	.02
Backwards counting[23]	2678	0.04 (-0.28 to 0.36)	.73
TICS total[c]	3063	-0.01 (-0.16 to 0.13)	.80
Composite score[d]	2636	0.03 (-0.14 to 0.19)	.66



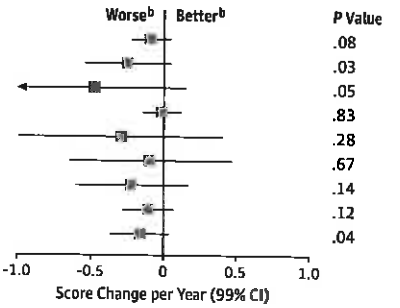
High Zinc vs Low Zinc[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	P Value
TICS word list recall[20]	2007	-0.02 (-0.14 to 0.11)	.74
Verbal fluency, animal[21]	2010	-0.23 (-0.50 to 0.05)	.04
Verbal fluency, letter[21]	2008	0.12 (-0.48 to 0.71)	.61
Verbal fluency, alternating[21]	2000	0.05 (-0.07 to 0.17)	.29
Wechsler logical memory I[22]	2009	-0.01 (-0.68 to 0.66)	.97
Wechsler logical memory II[22]	2006	-0.15 (-0.68 to 0.38)	.46
Backwards counting[23]	2007	0.00 (-0.36 to 0.37)	.98
TICS total[c]	2274	-0.01 (-0.18 to 0.16)	.89
Composite score[d]	1980	-0.02 (-0.21 to 0.17)	.77



Beta Carotene vs No Beta Carotene[a]

Test	No. of Patients	Difference in Change in Score per Year (99% CI)	P Value
TICS word list recall[20]	1795	-0.09 (-0.23 to 0.04)	.08
Verbal fluency, animal[21]	1798	-0.25 (-0.55 to 0.04)	.03
Verbal fluency, letter[21]	1796	-0.48 (-1.11 to 0.15)	.05
Verbal fluency, alternating[21]	1789	-0.01 (-0.14 to 0.12)	.83
Wechsler logical memory I[22]	1797	-0.29 (-0.99 to 0.41)	.28
Wechsler logical memory II[22]	1794	-0.09 (-0.65 to 0.46)	.67
Backwards counting[23]	1795	-0.22 (-0.61 to 0.17)	.14
TICS total[c]	2022	-0.11 (-0.28 to 0.07)	.12
Composite score[d]	1771	-0.16 (-0.36 to 0.04)	.04



LCPUFAs indicate long-chain polyunsaturated fatty acids.

[a] These analyses were adjusted for the following baseline covariates: age, sex, race, education, hypertension, baseline cognitive score, and baseline depression scale.

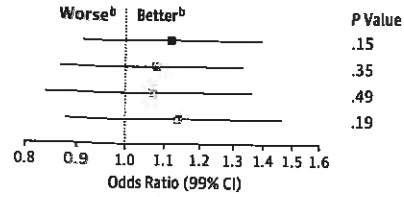
[b] Worse indicates a deterioration of the score for the tested nutrient (as indicated in each panel) and better means an improved score for participants randomized to receive the tested nutrient.

[c] The Telephone Interview Cognitive Status-Modified (TICS-M)[3] is a version of the Mini Mental State Examination (score range, 0-39 points; see eMethods [in Supplement 2] for explanation of scores for the other cognitive function tests).

[d] Composite scores were constructed by including the score of the cognitive tests, converting all test results into *z* scores, then adding the *z* scores. The composite score was computed to obtain an overall score for the battery of cognitive function tests, ranging from −22 to 17, with higher scores indicating better function.

Figure 3. Association of a TICS Score of Less Than 30 With Nutrient Intervention[a]

Nutrient	Score <30		Score ≥30		Odds Ratio (99% CI)	P Value
	No. of Patients	No. of Events	No. of Patients	No. of Events		
Omega-3 LCPUFA vs no omega-3 LCPUFA	1521	416	1503	397	1.12 (0.91-1.39)	.15
Lutein/zeaxanthin vs no lutein/zeaxanthin	1485	410	1539	403	1.08 (0.87-1.33)	.35
High zinc vs low zinc	1122	322	1123	303	1.07 (0.84-1.36)	.49
Beta carotene vs no beta carotene	999	289	996	261	1.14 (0.88-1.46)	.19



LCPUFAs indicate long-chain polyunsaturated fatty acids.

[a] Data were calculated using repeated-measures logistic regression. The Telephone Interview Cognitive Status-Modified (TICS-M)[3] is a version of the Mini Mental State Examination, (score range, 0-39 points). A dichotomous outcome from the TICS is defined as follows: (1) TICS total <30 points defines low cognitive function; and (2) TICS total ≥30 defines normal cognitive function. Models were adjusted for: baseline age, sex, race, history of hypertension, education, baseline cognitive score and baseline depression score.

[b] Worse indicates a deterioration of the TICS score (large proportion with low cognitive function) for that given nutrient and better indicates an improved TICS (smaller proportion with low cognitive function).

ranged from −0.32 to 0.41 and none were statistically significant (Figure 2B).

We also evaluated the data stratified by the dietary intake of omega-3 LCPUFAs and lutein with zeaxanthin. We found no difference among participants with varying dietary intake.

Interactions Between LCPUFAs and Lutein/Zeaxanthin

Studies of interaction were conducted to assess for potential interactions between omega-3 LCPUFAs and lutein/zeaxanthin. We found no statistically significant interaction between omega-3 LCPUFAs and lutein/zeaxanthin (TICS score, $P = .14$; composite score, $P = .98$).

Main Effects of High Zinc vs Low Zinc

The yearly change in the composite cognitive function score was −0.20 (99% CI, −0.27 to −0.13) for participants randomized to receive high zinc vs −0.19 (99% CI, −0.27 to −0.12) for those randomized to receive low zinc (difference in yearly change, −0.02 [99% CI, −0.21 to 0.17]; $P = .77$; Figure 2C). Similarly, the difference in the yearly TICS score change between the high and low zinc groups was −0.01 (99% CI, −0.18 to 0.16, $P = .89$; Figure 2C), and the odds of having TICS score of less than 30 was 1.07 (99% CI, 0.84 to 1.36; $P = .49$; Figure 3). The results of the tests ranged from −0.23 to 0.12 and none were statistically significant (Figure 2C).

Main Effects of Beta Carotene vs No Beta Carotene

The yearly change in the composite cognitive function score was −0.24 (99% CI, −0.32 to −0.16) for participants randomized to receive beta carotene vs −0.18 (99% CI, −0.26 to −0.10) for those randomized to not receive beta carotene (difference in yearly change of −0.16 [99% CI, −0.36 to 0.04]; $P = .04$; Figure 2D). Similarly, the difference in the yearly TICS score change between the beta carotene treatment groups was −0.11 (99% CI, −0.28 to 0.07; $P = .12$; Figure 2D), and the odds of having TICS score of less than 30 was 1.14 (99% CI, 0.88 to 1.46; $P = .19$; Figure 3). The results of the substudies ranged from −0.48 to −0.01 and none were statistically significant (Figure 2D).

Discussion

After a 5-year RCT, supplementing with omega3-LCPUFAs, specifically DHA and EPA (total, 1 g), and/or lutein, 10 mg, and zeaxanthin, 2 mg, did not have a statistically significant effect on cognitive function in this population of persons with intermediate AMD (bilateral large drusen) or late AMD in one eye. The results of the randomization to high zinc vs low zinc or beta carotene vs no beta carotene also showed no statistically significant effect. However, worse cognitive function at study entry was associated with increasing age, lower education level, and the male sex in our baseline cross-sectional data. Other medical risk factors such as hypertension and other cardiovascular disease including stroke were associated with lower cognitive function testing scores. During the course of the study, these same risk factors, as well as a lower baseline cognitive function test score, were also associated with greater decline in the cognitive function test scores—both the TICS and the composite score (Table 3).

The strengths of the study include the high adherence rates to the study supplements, as well as the high rates of cognitive function testing in a clinical trial with a relatively large study population. The interviewers underwent extensive training as well as periodic certification to ensure quality data. The battery of cognitive function tests in AREDS2, which was conducted over the telephone without visual input, is particularly appropriate for a population that has AMD. This battery of testing is similar to the battery used in other large-scale studies that used a similar telephone interview, especially using the TICS test, to evaluate cognitive function. These tests have been validated to give quality assessments.[28]

The limitations of this trial include the limited generalizability of the results because the study was conducted in a select population of well-nourished and highly educated persons with at least intermediate AMD or advanced AMD in one eye. This condition is also a neurodegenerative disease with limited information on its pathogenesis. Another limi-

tation of this study is the possibility that at nonphysiologic levels, the nutrients we tested have different biologic effects, different from those attained with dietary intake. It is possible that these supplements were started too late in the aging process since the mean age of the study population at baseline was 72.7 years. It is plausible that supplementation duration of 5 years may be insufficient, as suggested by the differential effects seen in the Physicians Health Study II (PHSYII) cognitive ancillary study in those participants who had 18 years of supplementation with beta carotene vs those with a much shorter duration of 1 year.[11] The process of cognitive decline may occur over decades, thus a short-term supplementation given too late in the disease may not be effective.

We attempted to evaluate the role of antioxidant vitamins and zinc in cognitive function testing in the original AREDS study, which was a placebo-controlled RCT.[9] A limitation of the original AREDS results, however, was that cognitive testing was not conducted at baseline, which left researchers unable to determine whether antioxidant or copper and zinc treatment influenced the rate of cognitive decline (although baseline cognition was likely identical across assigned treatment groups).

The observational data regarding dietary intake of specific nutrients such as omega-3 LCPUFAs and antioxidants suggest strong inverse associations with dementia, yet the RCTs have failed to show beneficial effects. It is possible that eating foods rather than taking any specific single supplement may have an effect. Similarly, observational data suggested a protective association of high levels of dietary omega-3 LCPUFAs for AMD, but the overall primary effects of the AREDS2 study on AMD also demonstrated that DHA/EPA had no effect on the treatment of AMD[15] while lutein/zeaxanthin had an incremental effect.[15,29] Similarly, we found that omega-3 LCPUFAs for the treatment of cardiovascular disease in AREDS2, another ancillary study, also did not result in a beneficial effect.[30] Studying dietary and food intake patterns rather than specific factors isolated with food source may better reflect nutritional benefits because we have no knowledge of the actual factor(s) that may make an effect or of the interactions between nutrients that influence the physiologic effects of any one nutrient that may target tissues or pathways.

Conclusion

Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.

ARTICLE INFORMATION

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Author Contributions: Drs Chew and Clemons had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Chew, Clemons, Agrón, Launer, Bernstein.
Drafting of the manuscript: Chew, Agrón.
Critical revision of the manuscript for important intellectual content: Chew, Clemons, Agrón, Launer, Grodstein, Bernstein.
Statistical analysis: Clemons, Agrón, Launer.
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Study supervision: Chew.

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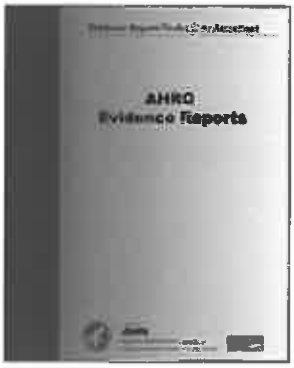

Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases

Evidence Reports/Technology Assessments, No. 114

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Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb.
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Structured Abstract

Context: It has been suggested that omega 3-fatty acids have beneficial effects in several conditions and disorders affecting the central nervous system, including providing a protective effect on cognitive function with aging; dementia, particularly senile dementia of the Alzheimer's type; multiple sclerosis and some of the peroxisomal biogenesis disorders.

Objectives: To assess the effect of omega-3 fatty acids on 1) cognitive function in normal aging 2) the incidence of dementia, 3) treatment of dementia, 4) the incidence of several neurological diseases, and 5) clinical outcomes related to the progression of multiple sclerosis.

Data Sources: We searched computerized databases to identify potentially relevant studies and contacted industry experts for unpublished data.

Study Selection: We screened 5,865 titles, reviewed 497 studies - of which 62 underwent a detailed review, and found 12 studies that pertained to our objectives. We included controlled clinical trials and observational studies, including prospective cohort, case-control, and case series designs; we excluded case reports. We had no language restrictions.

Data Extraction: We abstracted data on the effects of omega-3 fatty acids and on study design; relevant outcomes; study population; source, type, amount, and duration of omega-3 fatty acid consumption; and parameters of methodologic quality.

Data Synthesis: 1) A single cohort study has assessed the effects of omega-3 fatty acids on cognitive function with normal aging and found no association for fish or total omega-3 consumption. 2 and 3) In four studies (3 prospective cohort studies and one RCT) that assessed the effects of omega-3 fatty acids on incidence and treatment of dementia, a trend in favor of omega-3 fatty acids (fish and total omega-3 consumption) toward reducing risk of dementia and improving cognitive function was reported. 4) Two studies, one cohort and one case-control, that assessed the effects of omega-3 fatty acids on incidence of MS were inconclusive. A single cohort study evaluating the effects of omega-3 fatty acids on incidence of Parkinson's disease found no significant association between dietary intake of omega 3 fatty acids (fish, ALA, EPA, or DHA) and Parkinson's. Another single case-control study found a significant association between maternal fish consumption at least once a week throughout pregnancy and a lower risk of cerebral palsy in offspring. 5) In one RCT, omega-3 fatty acids (fish, ALA, EPA, DHA) had no effect on the progression of multiple sclerosis; two single-arm open-label trials showed improvement in disability with omega-3 supplementation.

Conclusions: The quantity and strength of evidence for effects of omega-3 fatty acids on the neurological conditions assessed vary greatly. Due to the small number of studies that met our inclusion criteria, further research is necessary before substantive conclusions can be drawn. The paucity of evidence in this area suggests that a great deal of epidemiological and clinical research remains to be done before any conclusions can be drawn or policy

recommendations can be made regarding the health effects of omega-3 fatty acids on normal cognitive function with aging, dementia, and neurological diseases.

Contents

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases was requested and funded by AHRQ. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.gov.

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1 Introduction

This report is one of a group of evidence reports prepared by three Agency for Healthcare Research and Quality (AHRQ)-funded Evidence-Based Practice Centers (EPCs) on the role of omega-3 fatty acids (both from food sources and from dietary supplements) in the prevention or treatment of a variety of diseases. These reports were requested by the National Institutes of Health Office of Dietary Supplements and several institutes at the National Institutes of Health (NIH). The three EPCs - the Southern California EPC (SCEPC, based at RAND), the Tufts-New England Medical Center (NEMC) EPC, and the University of Ottawa EPC - have each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of these reports is to summarize the current evidence on the effects of omega-3 fatty acids on prevention and treatment of cardiovascular diseases, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, immune-mediated diseases, tissue/organ transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

This report focuses on the effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Other reports from the SCEPC focus on cancer and immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases.

This chapter provides a brief review of the current state of knowledge about the metabolism, physiological functions, and sources of omega-3 fatty acids.

The Recognition of Essential Fatty Acids

Dietary fat has long been recognized as an important source of energy for mammals, but in the late 1920s, researchers demonstrated the dietary requirement for particular fatty acids, which came to be called essential fatty acids. It was not until the advent of intravenous feeding, however, that the importance of essential fatty acids was widely accepted: Clinical signs of essential fatty acid deficiency are generally observed only in patients on total parenteral nutrition who received mixtures devoid of essential fatty acids or in those with malabsorption syndromes. These signs include dermatitis and changes in visual and neural function. Over the past 40 years, an increasing number of physiological functions, such as immunomodulation, have been attributed to the essential fatty acids and their metabolites, and this area of research remains quite active.[1, 2]

Fatty Acid Nomenclature

The fat found in foods consists largely of a heterogeneous mixture of triacylglycerols (triglycerides)—glycerol molecules that are each combined with three fatty acids. The fatty acids can be divided into two categories, based on chemical properties: saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. The term "saturation" refers to a chemical structure in which each carbon atom in the fatty acyl chain is bound to (saturated with) four other atoms, these carbons are linked by single bonds, and no other atoms or molecules can attach; unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond, which allows the attachment of additional atoms to those carbons (resulting in saturation). Despite their differences in structure, all fats contain approximately the same amount of energy (37 kilojoules/gram, or 9 kilocalories/gram).

The class of unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Monounsaturated fatty acids (the primary constituents of olive and canola oils) contain only one double bond. Polyunsaturated fatty acids (PUFAs) (the primary constituents of corn, sunflower, flax seed, and many other vegetable oils) contain more than one double bond. Fatty acids are often referred to using the number of carbon atoms in the acyl chain, followed by a colon, followed by the number of double bonds in the chain (e.g., 18:1 refers to the 18-carbon monounsaturated fatty acid, oleic acid; 18:3 refers to any 18-carbon PUFA with three double bonds).

PUFAs are further categorized on the basis of the location of their double bonds. An omega or n notation indicates the number of carbon atoms from the methyl end of the acyl chain to the first double bond. Thus, for example, in the omega-3 (n-3) family of PUFAs, the first double bond is 3 carbons from the methyl end of the molecule. The trivial names, chemical names and abbreviations for the omega-3 fatty acids are detailed in Table 1.1.

Finally, PUFAs can be categorized according to their chain length. The 18-carbon n-3 and n-6 shorter-chain PUFAs are precursors to the longer 20- and 22-carbon PUFAs, called very-long-chain PUFAs (VLCPUFAs).

Fatty Acid Metabolism

Mammalian cells can introduce double bonds into all positions on the fatty acid chain except the n-3 and n-6 position. Thus, the shorter-chain alpha-linolenic acid (ALA, chemical abbreviation: 18:3n-3) and linoleic acid (LA, chemical abbreviation: 18:2n-6) are essential fatty acids. No other fatty acids found in food are considered 'essential' for humans, because they can all be synthesized from the shorter chain fatty acids.

Following ingestion, ALA and LA can be converted in the liver to the long chain, more-unsaturated n-3 and n-6 VLCPUFAs by a complex set of synthetic pathways that share several enzymes (Figure 1.1). VLC PUFAs retain the original sites of desaturation (including n-3 or n-6).

The omega-6 fatty acid LA is converted to gamma-linolenic acid (GLA, 18:3n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the longer-chain omega-6 fatty acid, arachidonic acid (AA, 20:4n-6). AA is the precursor for certain classes of an important family of hormone-like substances called the eicosanoids (see below).

The omega-3 fatty acid ALA (18:3n-3) can be converted to the long-chain omega-3 fatty acid, eicosapentaenoic acid (EPA; 20:5n-3). EPA can be elongated to docosapentaenoic acid (DPA 22:5n-3), which is further elongated, desaturated, and beta-oxidized to produce docosahexaenoic acid (DHA; 22:6n-3). EPA and DHA are also precursors of several classes of eicosanoids and docosanoids, respectively, are known to play several other critical roles, some of which are discussed further below.

The conversion from parent fatty acids into the VLC PUFAs - EPA, DHA, and AA - appears to occur slowly in humans. In addition, the regulation of conversion is not well understood, although it is known that ALA and LA compete for entry into the metabolic pathways.

Physiological Functions of EPA and AA

As stated earlier, fatty acids play a variety of physiological roles. The specific biological functions of a fatty acid are determined by the number and position of double bonds and the length of the acyl chain.

Both EPA (20:5n-3) and AA (20:4n-6) are precursors for the formation of a family of hormone-like agents called eicosanoids. Eicosanoids are rudimentary hormones or regulatory molecules that appear to occur in most forms of life. However, unlike endocrine hormones, which travel in the blood stream to exert their effects at distant sites, the eicosanoids are autocrine or paracrine factors, which exert their effects locally - in the cells that synthesize them or adjacent cells. Processes affected include the movement of calcium and other substances into and out of cells, relaxation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division, and growth.[3]

The eicosanoid family includes subgroups of substances known as prostaglandins, leukotrienes, and thromboxanes, among others. As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA (20:4n-6), is the precursor of a group of eicosanoids that include series-2 prostaglandins and series-4 leukotrienes. The omega-3 fatty acid, EPA (20:5n-3), is the precursor to a group of eicosanoids that includes series-3 prostaglandins and series-5 leukotrienes. The AA-derived series-2 prostaglandins and series-4 leukotrienes are often synthesized in response to some emergency such as injury or stress, whereas the EPA-derived series-3 prostaglandins and series-5 leukotrienes appear to modulate the effects of the series-2 prostaglandins and series-4 leukotrienes (usually on the same target cells). More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate the effects of excessive levels of series-2 prostaglandins. Thus, adequate production of the series-3 prostaglandins seems to protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma.[3]

EPA (0522:6 n-3) also affects lipoprotein metabolism and decreases the production of substances - including cytokines, interleukin 1β (IL-1β), and tumor necrosis factor α (TNF-α) - that have pro-inflammatory effects (such as stimulation of collagenase synthesis and the expression of adhesion molecules necessary for leukocyte extravasation [movement from the circulatory system into tissues]).[2] DPA (22:5n-3), the elongation product of EPA, is metabolized to DHA (22:6n-3). DHA (22:6n-3) is the precursor to a newly-described metabolite called 10,17S-docosatriene,[4] which is part of a family of compounds called 'resolvins.'[5] They are in the brain in response to an ischemic insult and counteract the pro-inflammatory actions of infiltrating leukocytes by blocking interleukin 1-beta-induced NF-kappaB activation and cyclooxygenase-2 expression.[6] DHA also plays a role in retinal rod outer segments by influencing membrane fluidity so as to optimize G protein coupled signaling.[7] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs and VLCPUFAs remains unknown, although suppression of omega-6-derived eicosanoid production by omega-3 fatty acids may be involved, because the omega-3 and omega-6 fatty acids compete for common enzymes in the fatty acid metabolic pathway, including delta-6 desaturase, as well as the rate-limiting enzymes in the eicosanoid pathway - phospholipases A2, cyclooxygenase, and lipoxygenase.

DPA (22:5n-3) (the elongation product of EPA) and its metabolite DHA (22:6n-3) are frequently referred to as very long chain n-3 fatty acids (VLCFA). Along with AA, DHA is the major PUFA found in the brain and is thought to be important for brain development and function. Recent research has focused on this role and the effect of supplementing infant formula with DHA (since DHA is naturally present in human breast milk but not in formula).

Dietary Sources and Requirements

Both ALA and LA are present in a variety of foods. LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA is present in some commonly used oils, including canola and soybean oil, and in some leafy green vegetables. Thus, the major dietary sources of ALA and LA are PUFA-rich vegetable oils. The proportion of LA to ALA as well as the proportion of those PUFAs to others varies considerably by the type of oil. With the exception of flaxseed, canola, and soybean oil, the ratio of LA to ALA in vegetable oils is at least 10 to 1. The ratios of LA to ALA for flaxseed, canola, and soy are approximately 1: 3.5, 2:1, and 8:1, respectively; however, flaxseed oil is not typically consumed in the North American diet. It is estimated that on average in the U.S., LA accounts for 89 percent of the total PUFAs consumed, and ALA accounts for 9 percent. Another estimate suggests that Americans consume 10 times more omega-6 than omega-3 fatty acids.[8] Table 1.2 shows the proportion of omega-3 fatty acids for a number of foods.

Several lines of research have suggested that the high ratio of omega 6s to low levels of omega-3 fatty acids currently consumed in the U.S. promotes a number of chronic diseases. Whether or not the relatively high intake of omega-6 fatty acids independently contributes to this problem[8] is currently uncertain. Because of the slow rate of elongation and further desaturation of the essential FA, the importance of VLC PUFAs to many physiological processes, and the overwhelming ratio of LA (omega 6s) to ALA (omega 3s) in the average U.S. diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of omega-3 VLC PUFAs by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of LC omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat

germ, and some dietary supplements, and the primary dietary sources of omega-6 VLC PUFAs are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994-98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main sources of dietary intake data for the U.S. population. The CSFII has the advantage of collecting dietary recall data over a period of several days, which may permit estimates of omega-3 intake that more accurately reflect individual intakes than do those of NHANES, which represent 24-hour dietary recalls. However, NHANES intake data have the advantage of being able to be linked to health outcomes. Table 1.3 provides a list of food sources of omega-3 fatty acids.

Table 1.4 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by NHANES III.[i] Table 1.5 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by CSFII.

Lacking sufficient evidence from research on the effects or correction of dietary deficiencies to establish Recommended Dietary Allowances (RDAs) for the essential fatty acids, the Food and Nutrition Board (FNB) of the Institute of Medicine[9] has set adequate intakes[ii] (AI) for the essential fatty acids, based on the average intakes of healthy CSFII participants. The AIs for the essential fatty acids vary by age group and sex, as well as for particular conditions such as pregnancy and breastfeeding. For ALA, the AI for men 19 and older, is 1.6 grams/day and the AI for (non-pregnant, non-breastfeeding) women is 1.1 grams/day. The AI for LA is 17 grams/day for men and 11 grams/day for women.

Based on evidence suggesting a role in prevention or treatment of some chronic diseases, the FNB has also established Acceptable Macronutrient Distribution Ranges (AMDR) for the essential fatty acids. An AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[9] The AMDR is expressed as a percentage of total energy intake: The AMDR for LA is set at five to 10 percent of usual energy intake, and the AMDR for ALA is 0.6 to 1.2 percent of energy intake. Of this amount, up to 10 percent can be consumed as EPA and/or DHA, the omega-3 VLC PUFAs. For a person who consumes 2000 kcal/day, ALA intake should range from 1.3 to 2.6 grams/day, and EPA/DHA intake can substitute for 0.13 to 0.26 of that quantity. Table 1.3 lists foods that provide 10 percent or more of these recommended intakes per serving, which may be referred to as "good sources."[iii] Table 1.6 provides the actual omega-3 content per 100 gm for a variety of foods.

Physiological Role of Omega-3 Fatty Acids in the Brain

About 50 to 60 percent of the dry weight portion of the human brain consists of lipids. PUFAs constitute approximately 35 percent of that lipid content.[10] Omega-3 fatty acids, particularly EPA and DHA, play important roles in the development and maintenance of normal central nervous system (CNS) structure and function. Along with the omega-6 fatty acid, AA, DHA is a major constituent of neuronal membranes, making up about 20 percent of the brain's dry weight.[11] Synapses contain a high concentration of DHA, which appears to play a role in synaptic signal transduction.[12] The metabolic pathways of the essential fatty acids that play an important role in neuronal signal transduction are schematically illustrated in Figure 1.2. Release of these fatty acids is involved in the phospholipase A_2 cycle following activation of various neurotransmitter receptors. DHA is also important for normal cognitive development.[13] In addition, the anti-inflammatory compounds for which DHA is a precursor may function in the brain to protect against ischemic damage. PUFAs in general play important roles in structural and functional maintenance of neuronal membranes, neurotransmission, and eicosanoid biosynthesis,[10, 14] as well as in the maintenance of membrane fluidity and flexibility and in the modulation of ion channels, receptors, and ATPases. The importance of PUFAs in maintenance of adequate membrane rigidity is evidenced by the loss of fluidity that follows decreased in PUFAs,[15, 16] leading to changes in the orientation and function of receptors and ion channels, such as calcium and sodium channels.[16]

Work in animal models has reported superior learning and memory in animals fed omega-3 fatty acids compared with control animals.[17, 18] In transgenic mouse models, dietary DHA improved memory, increased synapse density and decreased amyloid beta toxicity, thus providing evidence of protection against AD and cognitive decline.[19, 20]

Omega-3 Fatty Acids in Neurologic Disorders

Deficiencies in omega-3 FA and/or an imbalance in the ratio of omega-6 FA to omega-3 FA have been implicated in a variety of disorders affecting the CNS, including Alzheimer's disease (AD),[21–26] the peroxisomal biogenesis disorders (a collection of relatively rare neurological conditions, of which Zellweger's syndrome is one of the most common),[27–32] several psychiatric disorders,[9, 11, 13, 33] Parkinson's disease,[34, 35] amyotrophic lateral sclerosis (ALS),[36] Huntington's disease,[37–39] ischemic brain injury,[36] and multiple sclerosis (MS).[40–49] Indeed, dietary intake of omega-3 FA has been associated with a reduced incidence of MS since the early studies of Swank in the 1950s.[50]

Various animal and human studies have suggested several possible biological mechanisms for the role of FA in disease processes. Evidence for a positive association between intake of omega-3 FA and reduction of cardiovascular risk and adverse outcomes,[51] along with the finding that certain forms of dementia have been related to cardiovascular risk factors, suggest that one mechanism linking FA and cognitive function or dementia may be atherosclerosis and thrombotic events.[52] Inflammation is another mechanism that may explain the role that omega-3 fatty acids play in dementia.[53]

Several intervention trials in human infants have investigated the effects of omega-3 FA on cognitive development.[50, 54] Research has also shown these FA to be important in human infant visual development. A meta-analysis of several intervention trials showed that healthy pre-term infants who were administered DHA-supplemented formula had significantly higher visual resolution acuity at two and four months of age compared with infants fed DHA-free formula.[55]

However, few clinical intervention trials have examined the role of omega-3 FA in changes in cognitive function with aging and adult neurological conditions. The studies that have investigated the relationship between omega-3 FA intake and cognitive function, dementia, or other neurological diseases are mainly observational.

Rationale for and Organization of this Report

Epidemiological studies have suggested that groups of people who consume diets high in omega-3 FAs may experience a lower prevalence of certain neurological conditions, particularly cognitive impairment and dementia disorders. In addition, several studies have attempted to assess the effects of adding omega-3 FA to the diet, either as omega-3 FA-rich foods or as dietary supplements (primarily fish oils) in the treatment of certain neurological diseases, notably MS.

In response to this evidence, a number of omega-3 FA-containing dietary supplements that claim to protect against a variety of conditions have appeared on the market. Thus, AHRQ and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) have requested a synthesis of the research to date on the health effects of diets rich in omega-3 FA.

The remainder of this report is organized into four chapters. Chapter Two describes the methods we used to identify and review studies related to the role of omega-3 FA in cognitive function with aging, dementia, and other neurological diseases/conditions. We did not analyze any studies on the role of omega-3 fatty acids in stroke because this topic has been addressed by the New England EPC in their report on *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*. Chapter Three presents our findings related to the effects of omega-3 FA on those diseases/conditions. Chapter Four presents our conclusions and recommendations for future research in this area.

Footnotes

i The population represented by NHANES III includes individuals ages 2 months and older. Mexican Americans and non-Hispanic African-Americans, children 5 years old and younger, and adults 60 years of age and over were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall data. The NHANES III also included a physical examination and health survey of each participant.

ii

An Adequate Intake (AI) is defined as "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people, that are assumed to be adequate - used when a recommended dietary allowance cannot be determined."[9] An AI is set when data are insufficient or inadequate to establish an Estimated Average Requirement, on which the RDA is based, and indicate the need for more and better research. The EAR is "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group," based on a specific indicator or criterion of adequacy.

iii Identifying a food as a "good source" of a nutrient strictly means that one standard serving of the food supplies 10 to 19 percent of the Daily Value for that nutrient. The Daily Values are based on the FDA's Daily Reference Values, standards for the macronutrients (fats, protein, carbohydrates, and dietary fiber), which are similar, although not identical to the DRIs (RDAs) and are based on the amount of energy consumed per day (2000 kcal/d is the reference for calculating DVs). In the case of the PUFAs, no DVs have been established: For this report, the FNB's AIs and AMDRs, have been used instead.

Figures

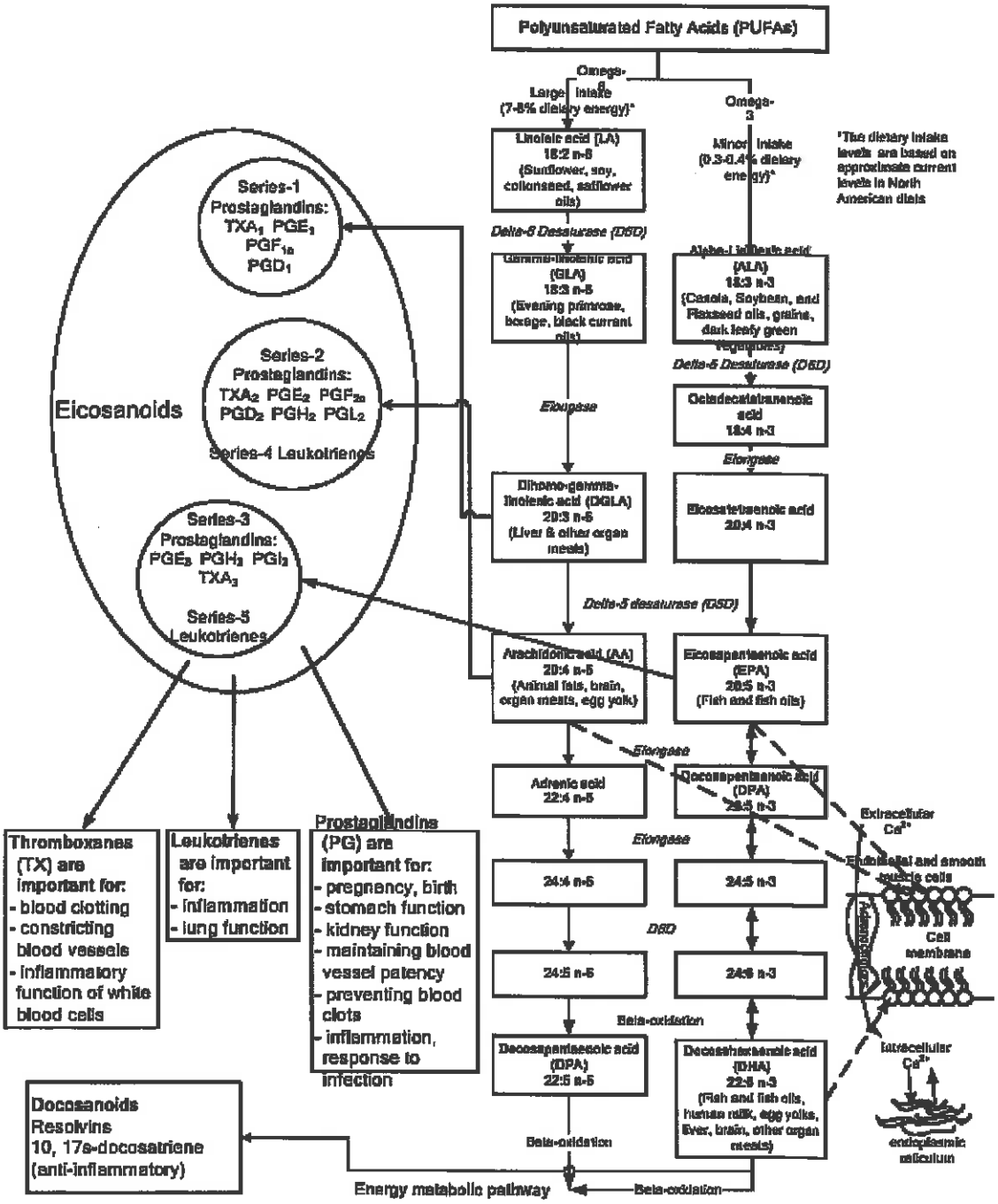

Figure 1. Classical Omega-3 and Omega-6 Fatty acid synthesis pathways and the role of omega-3 fatty acid in regulating health/disease markers

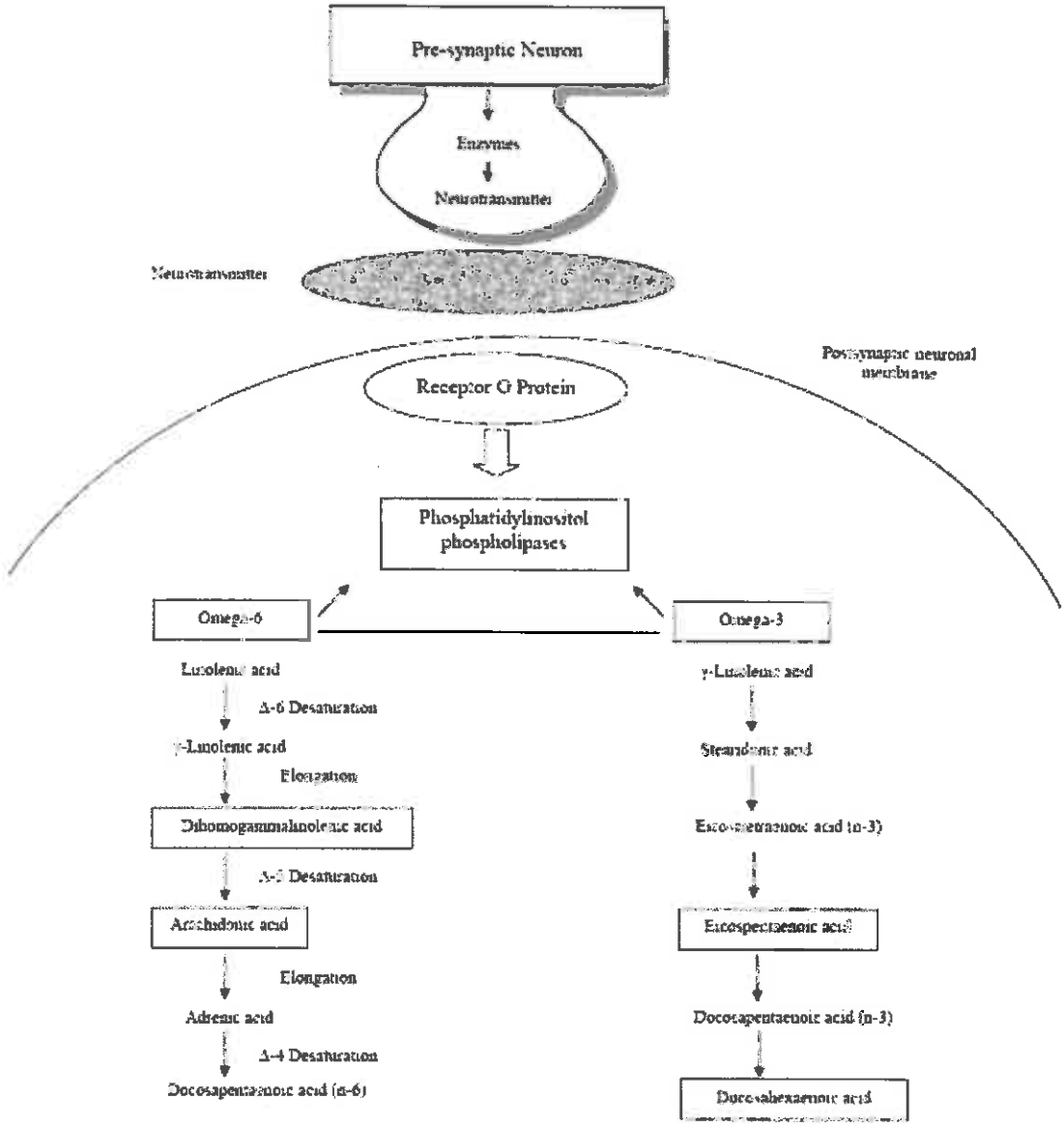

Figure 1.2 Schematic diagram illustrating the role of the metabolism of the essential fatty acids in neuronal signal transduction

Names		Abbreviations		
Trivial	**IUPAC***	**Carboxyl-reference**	**Omega-reference**	**Other**

Table 1.1 Nomenclature of omega-3 fatty acids

Names		Abbreviations		
Trivial	**IUPAC***	**Carboxyl-reference**	**Omega-reference**	**Other**
Linolenic acid	9, 12, 15-octadecenoic acid	$18:3\Delta^{9\,12\,15}$	18:3n-3	ALA
	alpha-linolenic acid		18:3 (ω-3)	α-LA
				LNA
				α-LNA
Docosahexaenoic acid	4, 8, 12, 15, 19- docosahexaenoic acid	$22:6\Delta^{4\,8\,12\,15\,19}$	22:6n-3	DHA
	cervonic acid		22:6 (ω-3)	
Docosapentaenoic acid	7, 10, 13, 16, 19- docosapentaenoic acid	$22:5\Delta^{7\,10\,13\,16\,19}$	22:5n-3	DPA
			22:5 (ω-3)	
Eicosapentaenoic acid	5, 8, 11, 14, 17- eicosapentaenoic acid	$20:5\Delta^{5\,8\,11\,14\,17}$	20:5n-3	EPA
Icosapentaenoic acid			20:5 (ω-3)	
Timnodonic acid				

* IUPAC=International Union of Pure and Applied Chemistry

Table 1.2 Sources and proportions of omega-3 fatty acids in common foods and supplements

Food/supplement	EPA 20:5n-3	DHA 22:6n-3	DPA 22:5n-3	ALA 18:3n-3
Food/supplement	**EPA**	**DHA**	**DPA**	**ALA**
	20:5n-3	**22:6n-3**	**22:5n-3**	**18:3n-3**
Food/Supplement in which Total Omega-3 Fatty Acids account for more than 50% of Total PUFA				
Fish				
Anchovy	✓	✓	✓	
Halibut	✓	✓	✓	
Herring	✓	✓	✓	
Mackerel	✓	✓	✓	
Salmon	✓	✓	✓	
Sardine	✓	✓	✓	
Tuna				
Canned, water packed	✓	✓	✓	
Fresh Bluefin	✓	✓	✓	
Oils/Supplements				
Cod liver oils	✓	✓	✓	
Coromega*	✓	✓		
Fish oil capsules*	✓	✓		
*Flaxseed/linseed oil**				✓
Herring oil	✓	✓	✓	
MaxEPA*	✓	✓		
Menhaden oil	✓	✓	✓	
Neuromins*		✓		
Omacor*	✓	✓		
Ropufa*	✓	✓	✓	
Salmon oil	✓	✓	✓	
Sardine oil	✓	✓	✓	
Seeds and other foods				
Flaxseeds/Linseeds				✓
Spinach, cooked				✓
Foods/Supplements in which total Omega 3 fatty acids are 10–50% of total PUFA				
Oils				
Black currant oil				✓
Canola oil†				✓
Mustard seed oils				✓

Food/supplement	EPA	DHA	DPA	ALA
	20:5n-3	22:6n-3	22:5n-3	18:3n-3
Soybean oil				✓
Walnut oil				✓
Wheat germ oil				✓
Other foods				
Wheat germ				✓
Human milk‡				✓
Foods/Supplements in which total omega 3 fatty acids are less than 10% of total PUFA				
Efamol Marine*	✓	✓		
Peanut butter				✓
Soybeans				✓
Olive oil				✓
Walnuts				✓

* Dietary Supplement;

† Also called rapeseed oil;

‡ The amounts of ALA, EPA, and DHA in human milk vary greatly as a function of maternal diet; the amount of DHA rarely seems to exceed 25 percent of the total n-3 PUFA content (ALA is present in the greatest amount), but that content as well as the proportion of DHA is assumed to meet the requirements of the infant.

Table 1.3 Good food sources* of omega-3 fatty acids

	EPA+DHA	ALA		EPA+DHA	ALA
Fish (3oz. Cooked)			**Oils (1 Tbs.)**		
Anchovy	✓		Canola		✓
Halibut	✓		Cod liver	✓	
Herring, Atlantic	✓		Flaxseed/linseed		✓
Pacific	✓		Herring	✓	
Mackerel, Atlantic	✓		Menhaden	✓	
Pacific	✓		Salmon	✓	
Salmon, Atlantic†	✓		Sardine	✓	
Sardines	✓		Soybean		✓
Trout, Rainbow	✓		Walnut		✓
Tuna, Albacore	✓		Wheat germ		✓
Canned light, water-packed	✓				
Canned white, water-packed	✓				
Fresh Bluefin	✓				
Organ Meats (3 oz. Cooked)			**Seeds**		
Brain, lamb	✓		Flaxseeds/linseeds (1 Tbs.)		✓
Brain, pork	✓				
Thymus, calf		✓			
Other Foods					
Caviar (1 oz.) ‡	✓				
Human breast milk (1c) ‡	✓§	✓			
Soybeans, cooked (1/2c)		✓			
Spinach, cooked (1/2c)		✓			
Tofu, regular (1/2c)		✓			
Walnuts (1/4c)		✓			
Wheat germ (1/4c) ‡		✓			

Source: Figures adapted from USDA, 2003;

9 Foods that provide (per serving) 10 percent or more of the Adequate Intake (AI) for ALA or the Acceptable Macronutrient Distribution Range (AMDR) for EPA and DHA (10 percent of the AMDR for ALA); an AI is a recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people (thus,

assumed to be adequate) when an RDA cannot be determined: an AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients.";

† Farm-raised Atlantic salmon have nearly identical omega-3 fatty acid levels to wild Atlantic salmon and significantly more omega-3 fatty acids than wild Pacific salmon;

‡ Standard serving size not established;

§ See table note for Table 1.2.

Table 1.4 Estimates of the mean intake of LA, ALA, EPA, and DHA in the U.S. Population from analysis of NHANES III data.*

	Grams/day		Percent energy intake/day	
	Mean ± SEM	Median (range)†	Mean ± SEM	Median (range)†
LA (18:2n-6)	14.1 ± 0.2	9.9 (0 – 168)	5.79 ± 0.05	5.30 (0 – 39.4)
ALA (18:3n-3)	1.33 ± 0.02	0.90 (0 – 17)	0.55 ± 0.004	0.48 (0 – 4.98)
EPA (20:5n-3)	0.04 ± 0.003	0.00 (0 – 4.1)	0.02 ± 0.001	0.00 (0 – 0.61)
DHA (22:6n-3)	0.07 ± 0.004	0.00 (0 – 7.8)	0.03 ± 0.002	0.00 (0 – 2.86)

* Based on analysis of a single 24-hour dietary recall from NHANES III data;

† Distributions are not adjusted for the over-sampling of Mexican -Americans, non-Hispanic African Americans, children five years old and under, and adults 60 years and over in the NHANES III dataset.

Table 1.5 Mean, range, and median usual daily intakes (ranges) of n-6 and n-3 PUFAs, in the U.S. population, from analysis of CSFII data (1994 to 1998).*

	Mean (gms/d) (± SEM)†	Range of Means (gms/d) (±SEM)	Median (gms/d) (± SEM)†
LA (18:2n-6)	13.0 ± 0.1	6.7 ± 0.1–17.6 ± 0.5	12.0 ± 0.1
Total n-3 FA	1.40 ± 0.01	0.72 ± 0.02 – 1.86 ± 0.04	1.30 ± 0.01
ALA (18:3n-3)	1.30 ± 0.01	0.72 ± 0.02 – 1.73 ± 0.04	1.21 ± 0.01
EPA (20:5n-3)	0.028	0.002 – 0.049	0.004
DPA (22:5n-3)	0.013	0.001 – 0.019	0.005
DHA (22:6n-3)	0.057 ± 0.018	< 0.0005 ± 0.001	0.046 ± 0.013

9 Source: Adapted from Dietary Reference Intakes Report;

* Estimates are based on respondents' intakes on the first day of survey and were adjusted using the Iowa State University method;

† For all individuals.

Food item EPA DHA ALA

Table 1.6 The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils.*

Food item	EPA	DHA	ALA
Fish (Cooked in dry heat unless otherwise specified)			
Anchovy, European	0.8	1.3	-
Bass, Freshwater, Mixed Sp.	0.3	0.5	0.1
Bass, Striped	0.2	0.8	trace
Bluefish	0.3	0.7	-
Carp	0.3	0.3	0.3
Catfish, Channel, farmed	trace	0.1	0.1
Cod, Atlantic	trace	0.2	trace
Cod, Pacific	0.1	0.2	trace
Eel, Mixed Sp.	0.1	0.1	0.6
Flounder & Sole Sp.	0.2	0.3	trace
Grouper, Mixed Sp.	trace	0.2	-
Haddock	0.1	0.2	trace
Halibut, Atlantic and Pacific	0.1	0.4	0.1
Halibut, Greenland	0.7	0.5	0.1
Herring, Atlantic	0.9	1.1	0.1
Herring, Pacific	1.2	0.9	0.1
Mackerel, Atlantic	0.5	0.7	0.1
Mackerel, Pacific and Jack	0.7	1.2	0.1
Mullet, Striped	0.2	0.1	trace
Ocean Perch, Atlantic	0.1	0.3	0.1
Pike, Northern	trace	0.1	trace
Pike, Walleye	0.1	0.3	trace
Pollock, Atlantic	0.1	0.5	-
Pompano, Florida	0.2	0.5	-
Roughy, Orange	trace	-	trace
Salmon, Atlantic, Farmed	0.7	1.5	0.1
Salmon, Atlantic, Wild	0.4	1.4	0.4
Salmon, Chinook	1.0	0.7	0.1
Salmon, Chinook, Smoked(lox)	0.2	0.3	-
Salmon, Chum	0.3	0.5	trace
Salmon, Coho, Farmed	0.4	0.9	0.1
Salmon, Coho, Wild	0.4	0.7	0.1
Salmon, Pink	0.4	0.6	trace

Food item	EPA	DHA	ALA
Salmon, Pink, Canned	0.8	0.8	0.1
Salmon, Sockeye	0.5	0.7	0.1
Sardine, Atlantic, Canned in Oil	0.5	0.5	0.5
Sea bass, Mixed Sp.	0.2	0.6	-
Seatrout, Mixed Sp.	0.2	0.3	trace
Shark, Mixed Sp., battered and fried	0.3	0.4	0.2
Snapper, Mixed Sp.	0.1	0.3	0.1
Swordfish	0.1	0.7	0.2
Trout, Mixed Sp.	0.3	0.7	0.2
Trout, Rainbow, Farmed	0.3	0.8	0.1
Trout, Rainbow, Wild	0.5	0.5	0.2
Tuna, Fresh, Bluefin	0.4	1.1	-
Tuna, Fresh, Skipjack	trace	0.2	-
Tuna, Fresh, Yellowfin	trace	0.2	trace
Tuna, Light, Canned in Oil	trace	0.1	trace
Tuna, Light, Canned in Water	trace	0.2	trace
Tuna, White, Canned in Oil	trace	0.2	0.2
Tuna, White, Canned in Water	0.2	0.6	trace
Whitefish, Mixed Sp.	0.4	1.2	0.2
Whitefish, Mixed Sp., Smoked	trace	0.2	-
Wolf fish, Atlantic	0.4	0.4	trace
Shellfish (Raw)			
Abalone, Mixed Sp., fried	0.1	0.1	0.1
Clam, Mixed Sp., moist heat	0.1	0.1	trace
Crab, Alaska King, moist heat	0.3	0.1	-
Crab, Blue, moist heat	0.2	0.2	-
Crayfish, Mixed Sp., Farmed	0.1	trace	trace
Lobster, Northern, moist heat	0.1	trace	trace
Mussel, Blue	0.3	0.5	trace
Oyster, Eastern, Farmed	0.2	0.2	0.1
Oyster, Eastern, Wild	0.3	0.3	0.1
Oyster, Pacific	0.9	0.5	0.1
Scallop, Mixed Sp.	0.2	0.2	-
Shrimp, Mixed Sp.	0.2	0.1	trace
Squid, Mixed Sp., fried	0.2	0.4	0.1
Fish Oils			

Food item	EPA	DHA	ALA
Cod Liver Oil	6.9	11.0	0.9
Herring Oil	6.3	4.2	0.8
Menhaden Oil	13.2	8.6	1.5
Salmon Oil	13.0	18.2	1.1
Sardine Oil	10.1	10.7	1.3
Nuts and Seeds			
Butternuts, Dried	-	-	8.7
Flaxseed			18.1
Walnuts, English	-	-	9.1
Plant Oils			
Canola (Rapeseed)	-	-	9.3
Flaxseed Oil	-	-	53.3
Soybean Lecithin Oil	-	-	5.1
Soybean Oil	-	-	6.8
Walnut Oil	-	-	10.4
Wheatgerm Oil	-	-	6.9

Source: Figures adapted from USDA, 2003;

* Sp = species.

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

2 Methodology

Objectives

The topic of this report was nominated by the NIH ODS. The three participating Evidence-Based Practice Centers (EPCs) were asked to examine the effects of omega-3 fatty acids, in general, and on the following conditions: Cardiovascular Disease, Transplantation, Immune-Mediated Diseases, Gastrointestinal/Renal Diseases, Cancer, Neurological conditions, Asthma, Child/Maternal Health, Eye Health, and Mental Health. The Southern California EPC (SCEPC) was responsible for examining Immune-Mediated Diseases and Gastrointestinal/Renal Diseases in Year-one of the project and Cancer and Neurological conditions in Year-two of the project.

Scope of Work

The methodology that we used for this study included the following:

- Refining the preliminary questions provided by AHRQ,
- Convening a technical expert panel to advise the SCEPC on the study,
- Identifying sources of evidence in the scientific literature,
- Establishing inclusion/exclusion criteria for the studies identified in the scientific literature,
- Identifying potential evidence with attention to controlled clinical trials using omega-3 fatty acids,
- Evaluating potential evidence for methodological quality and relevance,
- Extracting data from studies meeting methodological and clinical criteria,
- Synthesizing the results,
- Performing further statistical analysis on selected studies, as appropriate,
- Performing meta-analyses where appropriate,
- Submitting the results to technical experts for peer review,
- Incorporating reviewers' comments into a final report for submission to AHRQ.

Original Proposed Key Questions

Preliminary questions for the project were developed by ODS in collaboration with the following NIH Institutes: (a) National Cancer Institute (NCI); (b) National Eye Institute (NEI); (c) National Heart, Lung, and Blood Institute (NHLBI); (d) National Institute of Alcohol Abuse and Alcoholism (NIAAA); (e) National Institute of Allergy and Infectious Diseases (NIAID); (f) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); (g) National Institute of Child Health and Human Development (NICHD); (h) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); (i) National Institute of Mental Health; and (j) National Institute of Neurological Disorders and Stroke (NINDS). The general and disease-specific questions that were originally proposed are detailed in Appendix A.1.

Technical Expert Panel

Each AHRQ evidence report is guided by a Technical Expert Panel (TEP). The TEP advises the SCEPC on refining the preliminary questions, determining the proper inclusion/exclusion criteria for the studies, determining populations of interest, establishing proper outcome measures, and conducting appropriate analyses.

We convened a TEP that focused on neurological diseases and conditions. The TEP was composed of distinguished basic scientists and clinicians, with established expertise in omega-3 FA, human nutrition, dietary assessment methods, and neurology. In addition to the experts that we identified, AHRQ and the NIH Institute of Neurological Disorders and Stroke (NINDS) and Institute on Aging (NIA) recommended a number of industry experts. The members of our technical expert panel are listed by name along with a summary of their key comments and recommendations in Appendix A.2.

Key Questions Addressed in this Report

Based on input from our TEP, the preliminary disease-specific questions were revised. The questions that are addressed in this report are as follows:

- What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function in normal aging?
- What is the evidence that omega-3 fatty acids affect the incidence of dementia including Alzheimer's disease?
- What is the evidence that omega-3 fatty acids are effective in the treatment of dementia including Alzheimer's disease?
- What is the evidence that omega-3 fatty acids affect the incidence of neurological diseases?
- What is the evidence that omega-3 fatty acids prevent the progression of multiple sclerosis?

Identification of Literature Sources

Potential evidence for our study came from three sources: on-line library databases, the reference lists of all relevant articles, and industry experts.

Jessie McGowan, Senior Information Scientist, and Nancy Santesso, Knowledge Translation Specialist, at the University of Ottawa were responsible for developing a common search strategy for omega-3 FA for the 3 participating EPCs. Nancy Santesso developed a core omega-3 search strategy in collaboration with project librarians, biochemists, nutritionists, and clinicians, who also provided biochemical names, abbreviations, food sources, and commercial product names for omega-3 FA. The literature search was not restricted by language of publication or by study design, in order to increase sensitivity. When possible, the searches were limited to studies involving human subjects. The core search strategy is detailed in Appendix A.4.

For the SCEPC, this core search strategy was incorporated into a search for cognitive function with aging, Alzheimer's disease, and other neurological diseases/conditions. The strategy for this search is detailed in Appendix A.4.

The following databases were searched: Medline (1966-2003), Premedline (December, 2003), Embase (1980-2003), Cochrane Central Register of Controlled Trials (4th Quarter, 2003), CAB Health (1973-2003), Dissertation Abstracts (1861-2003). All of these databases were searched using the Ovid interface, except CAB Health, which was searched through SilverPlatter. Any duplicate records were identified and removed within each search question using Reference Manager software. The citations obtained from these literature searches were sent to the SCEPC via e-mail.

Two experienced reviewers, Walter Mojica and Amalia Issa, who were blinded to study authors and sources independently evaluated the citations and corresponding abstracts, if available. The reviewers selected article titles that focused on omega-3 FA and normal cognitive function with aging, dementia, and other neurologic diseases/conditions. In addition, they selected article titles that pertained to the disease conditions of the other participating EPCs. Language was not a barrier to inclusion. Articles that either reviewer selected were ordered, as well as those articles whose relevance could not be determined from the title or abstract. The articles were ordered from the UCLA library, or

Infotrieve, a Los Angeles-based literature retrieval firm with contacts around the world. The literature was tracked using ProCite and Access software.

In addition, we sent letters to industry experts recommended by the ODS to obtain any unpublished data (Figure A.3.1).

Evaluation of Evidence

Two experienced reviewers, Walter Mojica and Amalia Issa, independently reviewed each article that was ordered, to determine whether it should be accepted for further study, using a structured screening form (shown in Figure B.1, Appendix B) that included a defined set of inclusive/exclusive criteria (Table A.5.1, Appendix A.5). Walter Mojica is a physician with extensive experience in the science of systematic reviews and evidence-based medicine. Amalia Issa is a clinical neuroscientist with a background in AD research. Briefly, human controlled clinical trials (randomized and non-randomized), prospective cohort studies, case-control studies and case series were included; case reports were excluded. For inclusion, studies also had to describe assessing a difference between omega-3 fatty acids content in study arms for all study designs except case series, and describe the effect of omega-3 fatty acids on any of the following outcomes: cognitive decline with normal aging, incidence of dementia, progression of dementia, incidence of neurological disease, progression of MS. The reviewers resolved any disagreements by consensus. Reviewers were blinded to author and journal when reviewing titles and abstracts, but not when reviewing articles.

Extraction of Data

For the studies that passed our screening criteria, two reviewers independently abstracted detailed data onto a specialized quality review form (QRF) (Figure B.2, Appendix B).

Walter Mojica and Amalia Issa independently reviewed all of the studies. The reviewers resolved differences through consensus, and a senior physician researcher, Catherine MacLean, resolved any disagreements that could not be resolved through this method.

The QRF included questions about the study design; the outcomes of interest; study sample characteristics; details on the intervention, such as the dose, frequency, and duration; adverse events; the elapsed time between the intervention and outcome measurements, and, the types of outcome measures.

We consulted with several outside scientists to complete QRFs for foreign-language articles. Foreign language articles were reviewed as follows. Spanish-language articles were reviewed by Walter Mojica, French-language articles by Amalia Issa who are fluent in these languages. For other foreign-language articles, a single reviewer who is fluent in the language worked with Catherine MacLean to complete the standard abstraction form.

Grading Evidence

Methodologic Quality of Randomized Controlled Trials

To evaluate the quality of the design and execution of trials, we also collected information about the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts, and concealment of allocation. A score for quality was calculated for each trial using a system developed by Jadad (Appendix A.6, Figure A.6.1). The Jadad score rates studies on a scale of 0 to 5. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.[56] Thus, studies with a Jadad score of 3 or more are referred to as "high quality," and studies scoring 2 or less are referred to as "poor quality." For our purposes, if a trial was associated with more than one study, its quality score was equal to the maximum score calculated across its associated studies. Additionally, a generic summary quality score (A, B, C) was assigned to each study based on the combination of its Jadad score and reporting of concealment of allocation (Appendix A.6, Table A.6.1).

Methodologic Quality of Observational Studies

To evaluate the quality of the design and execution of observational studies, we collected information about the validity of ascertainment of cases and exposure, description of withdrawals and dropouts, and adjustment for confounders and blinded assessment of exposure and case status when ascertaining case and exposure status, respectively.[57, 58] We also described whether exposure occurred prior to the outcome, whether study groups were comparable, and whether there appeared to be selection bias. A score for quality was not calculated for observational studies, as there is no validated method to do so.

Applicability

This report focuses on the U.S. population as a whole. To capture the potential applicability of studies to the different populations of interest as defined in the scope of work (namely aging Americans or Americans with dementia or other neurological diseases/conditions), we categorized the populations in the studies we reviewed in terms of 1) applicability to the U.S. population and 2) health state (Appendix A.6, Table A.6.2). In the summary tables, each study receives a combined applicability grade based on the applicability and health state.

Data Synthesis

Because too few studies were identified to perform pooled analyses (meta-analysis), we performed a qualitative synthesis of the evidence.

This report is organized by five different study questions. For each study question we describe the number and design of studies identified that pertained to the question and describe the overall effect of omega-3 fatty acids across the studies. We describe the unit of analysis for omega-3 consumption, i.e. fish, total omega-3, DHA, EPA or ALA. We summarized the point estimates and statistical testing that were described in the original studies and state when these parameters were not reported. We specifically comment on whether the studies assessed the effects of omega-3 fatty acids on sub-populations, the effects of covariates on outcomes, the effects of omega-3 fatty acid source, dose and exposure duration and sustainment of effect after treatment with omega-3 fatty acids. When these parameters were assessed they were described. We also describe the quality and applicability of the studies for each topic. Of note, we describe whether information on covariates was reported in two ways and for two reasons. First, we report whether covariates had a specific effect on the outcome of interest and the magnitude of the effect if it was significant. Second, we report whether there was adjustment for covariates as a measure of methodologic quality.

Peer Review

This draft report was sent for review to a select group of experts in omega-3 fatty acids, epidemiology, nutrition, and cancer. The names, expertise, and affiliations of the peer reviewers are listed in Table A.7.1, Appendix A. Additionally, this draft report was sent to the members of the TEP for review. Service as a peer reviewer or as a technical expert panelist does not imply agreement or endorsement of the findings of this report.

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

3 Results

Results of Literature Search

Figure 3.1 displays the flow of the literature review. The University of Ottawa EPC e-mailed us 5,848 citations as a result of their computerized library searches, our reviewers found 17 additional citations as a result of reference mining, and peer reviewers suggested three citations not identified by these sources for a total of 5,868 citations. Our two reviewers considered 505 of these article titles to be relevant to our research topics. We were able to retrieve 500 (99%) of these articles.

Of the 500 articles retrieved, 438 were rejected (Figure 3.1). We identified 62 studies that passed the preliminary screening criteria and went on to the QRF stage. At this stage of review, we further excluded studies from our final analysis set based on study design and whether the study assessed effects of omega-3 fatty acids on topics relevant to this report, i.e. the incidence and treatment of dementia, cognitive decline with normal aging, the incidence of other neurological diseases, and the progression of MS. Among the 62 studies reviewed with a QRF, 50 were rejected. Among the rejected studies, six had no difference in omega-3 fatty acid content among study arms. The other 44 articles that were rejected did not describe a condition, population, or outcome that was relevant to this report. The remaining 12 articles met our inclusion criteria and are described in detail in this report.

Effects of Omega-3 Fatty Acids

Summaries of all evaluated neurological studies can be found in Appendix C (Tables C.1 through C.4).

Cognitive Function in Normal Aging

Overall effect. We identified one study that evaluated the effect of omega-3 FA on cognitive function in community-dwelling elderly persons. This study[59] investigated the association between omega-3 FA and cognitive function in a cohort of 818 community-dwelling men (ranging in age from 64 to 84 years old) living in the Dutch town of Zutphen, who were participants in the Zutphen Elderly Study, a longitudinal study on risk factors for various chronic diseases. Data about dietary intake were collected by trained interviewers in 1985, 1990, and 1993, and data about cognitive function were collected in 1990 and 1993. Complete dietary information was collected on 476 men, and complete information regarding cognitive function was collected on 342 men. The relationship between both fish consumption and total omega-3 fatty acid consumption and both cognitive impairment and cognitive decline were assessed. Cognitive impairment was defined as a MMSE score ≤ 25; cognitive decline was defined as a drop of more than two points in the MMSE over a 3-year period, which corresponds to the 15th percentile of change. Compared with no fish consumption, fish consumption was inversely associated with cognitive impairment in crude analyses, but not after adjustment for multiple variables (Table 3.1). Fish consumption was also inversely associated with development of cognitive decline, though not significantly so (Table 3.1). Total omega-3 fatty acid consumption was not related to cognitive impairment or cognitive decline (Table 3.1).

Sub-populations. This study did not evaluate the differential effects of omega-3 FA on distinct subpopulations.

Covariates. Although analyses adjusted for a number of different covariates in a multivariable regression model (Table 3.1), the effects of specific covariates on the association between omega-3 fatty acid consumption and cognitive function were not described.

Effects of source, dose, and exposure duration

Source: This study assessed omega-3 fatty acid effects in terms of fish consumption and total omega-3 fatty acid consumption. Fish consumption was associated with a reduced risk of cognitive impairment but had no association with cognitive decline; omega-3 fatty acid consumption was not associated with either outcome.

Dose: Dose effect was not assessed for fish. A dose effect was observed for omega-3 fatty acid consumption and cognitive impairment on unadjusted analyses (p for trend = 0.9), but not on adjusted analyses. No dose effect was found with omega-3 fatty acid consumption and cognitive decline.

Exposure Duration: Effects of exposure duration were not assessed.

Sustainment of Effect. Sustainment of effect was not reported.

Quality and Applicability. Parameters of methodologic quality are as follows:

This study adjusted for confounders, had valid ascertainment of exposures and outcomes, ascertained that exposure occurred before outcome measurement, and described withdrawals and drop outs. It did not blind to exposure/outcome and did not describe selection bias.

This study had an applicability rating of II because the population sampled included only males. Thus, although this study represented a relevant sub-group of the target population, it was not representative of the entire target population because of its exclusive sampling of one gender.

Incidence of Dementia

Overall effect. We identified three prospective cohort studies[21, 23, 67] that evaluated the effect of omega-3 FA on the incidence of dementia (Table 3.2). All three of the studies assessed the incidence of dementia relative to fish consumption; one also assessed risk relative to total omega-3 fatty consumption and relative to consumption of ALA, EPA, and DHA, individually.[23] Fish intake was associated with a significant reduction in the incidence of non-Alzheimer's dementia in all three studies,[21, 67] although in one,[21] statistical significance was barely lost with multivariable adjustment[21] (Table 3.2). Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies; the association was statistically significant in one[67] and nearly so in the other two[21, 23] (Table 3.2). Total omega-3 fatty acid consumption and consumption of DHA were associated with a significant reduction in the incidence of Alzheimer's disease; consumption of ALA and EPA were not[23] (Table 3.2).

Sub-populations. One study assessed whether gender modified the effect of total omega-3 fatty acid consumption or consumption of fish, ALA, EPA, or DHA.[23] Total intake of omega-3 fatty acids was protective in females only (p for interaction= 0.02); gender did not modify the effect of fish, ALA, EPA, or DHA.

Covariates. Two of the studies[23, 67] assessed the influence of covariates on the effect of omega-3 FA on incidence of dementia.

In one study,[23] the multivariable relative risks for intakes of total omega-3 fatty acids, DHA, and EPA did not change when adjusted for vitamin E intake, other fat intake, and cardiovascular disease. In the same study, multivariable risks for intake of ALA were reported as approximately 1.0 with adjustment for vitamin E but not affected by adjustment for cardiovascular disease; intake of ALA was strongly protective among people with the APO-E-4 genotype (RR = 0.08 per natural log {milligram} increase in ALA, p = 0.02).

In the other study,[67] estimates of relative risk did not change with adjustment for cigarette smoking, alcohol consumption, fiber consumption, antioxidant intake, stroke, myocardial infarction, or serum total and high-density lipoprotein cholesterol.

Effects of source, dose, and exposure duration

Source: Fish consumption was associated with a significantly reduced risk of dementia in three of the studies.[21] In the one study that assessed the effect of total omega-3 fat consumption, ALA, DHA, and EPA on the incidence of dementia,

total omega-3 and DHA were associated with significant reduced risk in multivariable analyses; ALA and EPA were not.

Dose: Dose effects were observed for fish in one study[67] and for total omega-3 consumption and DHA in another[23] (p for trend <0.05 for each) (Table 3.2).

Exposure Duration: None of the studies addressed exposure duration.

Sustainment of effect. Sustainment of effect was not assessed in any of the studies.

Quality and applicability. Among these three studies, all adjusted for confounders, reported using valid methods to ascertain outcomes, and confirmed that the exposure occurred prior to the outcome.

One study did not describe a valid method to ascertain dietary intake[21] (method used was not described). One of the studies explicitly described whether the investigators were blinded to information on exposure when obtaining data on outcome or on outcome when obtaining data on exposure.[23, 34, 61]

Of the three studies, two[23, 67] had an applicability rating of I (applicable to the general target population of adults). One study received an applicability rating of II because it was performed in France.[21]

Treatment of Dementia

Overall effect. We identified one study[24] that assessed the efficacy of omega-3 FA as a treatment for dementia. This RCT assessed the effect of supplementation with DHA on cognitive function among 20 elderly nursing home residents with vascular dementia. Cognitive functioning was evaluated using Hasegawa's Dementia rating scale (HDS-R) and MMSE scores at baseline, and after 3, 6, and 12 months. Baseline Hasegawa's Dementia rating scale and MMSE scores were 15 to 22, consistent with mild to moderate dementia. HDS-R and MMSE scores improved in the DHA-treated group but not among patients who were not treated with DHA (Table 3.3). Comparisons between groups were significant at 3 and 6 months for the HDS-R and at 6 months for the MMSE.

Sub-populations. The study did not evaluate the differential effects of omega-3 FA on distinct subpopulations.

Covariates. The study did not evaluate covariates.

Effects of source, dose, and exposure duration

Source: The source assessed was DHA.

Dose: A single dose of 4.3 g of DHA was administered; dose effect was not assessed.

Exposure Duration: The duration of exposure was 12 months. Significant differences between study groups were observed after 3 months and after 6 months, but not after 12 months.

Sustainment of effect. Sustainment of effect was not assessed in either report.

Quality and applicability. Although this trial is described as randomized, the randomization is not described as double-blind, and there is no description regarding blinding or withdrawals/dropouts. The study[24] had an applicability rating of II with a summary quality score of C (Jadad score = 1; concealment of allocation was not reported); thus it can be considered of poor quality (Table 3.4).

Incidence of Neurological Diseases

Overall effect. We identified four studies[34, 43, 60, 61] that specifically addressed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia: two assessed the incidence of MS,[43, 61] one assessed the risk of Parkinson's disease,[34] and one assessed the risk of cerebral palsy[60] (Table 3.6).

The relationship between dietary intake of omega-3 FA and incidence of MS was assessed in two reports; one pooled data from two large cohorts of women from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II),[61] and the other used a case-control design.[43] The prospective cohort study assessed the effect of omega-3 fatty acids in terms of fish consumption, fish omega-3 FA, ALA, EPA, and DHA (Table 3.6). ALA was associated with a reduced risk of MS in both cohorts that did not reach statistical significance (pooled RR = 0.3; 95% C.I. 0.1–1.1) (Table 3.6). Intakes of omega-3 FA, EPA, or DHA were not associated with MS incidence. Relative risk estimates pooled for both NHS and NHS II cohorts for omega-3 FA intake (fish) were 1.1 (95% C.I. 0.9–1.3), for EPA intake, 1.3 (95% 0.9–1.9), and 1.1 (95% C.I. 0.9–1.5) for DHA intake (Table 3.6). The case-control study[43] evaluated 197 incident MS cases and 202 age-, sex- and neighborhood-matched controls and found no significant association between fish consumption and risk of MS overall (OR = 0.91, 95% C.I. 0.78–1.05). However, fish consumption was significantly associated with a lower risk of MS in females only (OR = 0.83, 95% C.I. 0.69–1.00; $p<0.05$) (Table 3.6).

The relationship between dietary intake of omega-3 FA and incidence of Parkinson's disease was assessed in one report that pooled data from two large prospective cohorts, the Health Professionals Follow-up Study and the Nurses' Health Study. This study assessed the effect of omega-3 FA in terms of omega-3 fats from fish, ALA, EPA, and DHA over a six- to eight-year period (Table 3.6). There was no significant association between fish omega-3 FA, ALA, EPA, or DHA intake and risk of Parkinson's disease (p for trend = 0.9, 0.9, 0.9 and 0.8, respectively).

In a pooled analysis of men and women across two cohorts, ALA was associated with a reduced risk of developing Parkinson's disease (RR = 0.65, 95% CI 0.46, 0.91 for comparison of highest to lowest quintiles of risk). Among women, there was a significant trend but no significant risk reduction for any individual quintile of consumption. This finding is particularly noteworthy given the statistical power of the Health Professionals Follow-up Study and the Nurses' Health Study and the longitudinal analysis of dietary intake in these studies.

One study[60] evaluated the effects of maternal dietary intake on the risk of cerebral palsy in offspring in a case-control study of 91 cases of cerebral palsy identified from statistics of hospitals and rehabilitation centers in Greece and 246 neighborhood controls. Mothers of cases and controls were interviewed about their dietary habits during pregnancy using a food-frequency questionnaire. Consumption of fish once a week throughout pregnancy was associated with a lower risk of cerebral palsy (OR= 0.63, 95% C.I. 0.37–1.08; $p < 0.09$) compared with no fish intake.

Sub-populations. Two studies[34, 43] stratified the effects of omega-3 FA by gender. The study that investigated the relationship between dietary intake of fat and Parkinson's disease found no apparent association between omega-3 FA intake and risk of Parkinson's disease for either males or females (p for trend = 0.9 for males and 0.8 for females).

In the other study,[43] which used a case-control design, fish consumption was associated with a reduced risk of MS among females, (OR = 0.83, 95% C.I. 0.69–1.00) but not males (OR = 1.08, 95% C.I. 0.84–1.40) (Table 3.6).

Covariates. Effects of any specific covariates on the observed omega-3 associations were not reported in any of the studies.

Effects of source, dose, and exposure duration

Source: The effect of fish consumption on the incidence of two different neurological diseases was assessed in three different reports. Fish consumption was associated with a reduced risk of cerebral palsy;[60] it had no overall effect on the incidence of MS in two studies,[43, 61] but was associated with a reduced risk for women in one.[43] Omega-3 FA from fish had no effect on the incidence of MS[43] or Parkinson's disease.[34] ALA was associated with a reduced risk of MS in one study[61] and had no effect on the incidence of Parkinson's disease in another.[34] EPA and DHA had no effect on the incidence of MS[61] or Parkinson's disease.[34]

Dose: Dose effect was assessed in two studies.[34, 61] One study[34] assessed the effect of fish dose on the incidence of MS and found no dose (or other) effect. A dose effect for ALA on the incidence of MS was reported in one study,[34] but no dose effect for ALA on the incidence of Parkinson's disease was found in the other study.[61] There was no dose effect for EPA or DHA in either study.

Exposure Duration: None of the studies assessed the effect of exposure duration.

Sustainment of effect. Sustainment of effect was not assessed in any of the reports.

Quality and applicability. Parameters of methodologic quality are detailed in Table 3.5. All four of the studies[34, 43, 60, 61] had an applicability rating of II.

Progression of Multiple Sclerosis

Overall effect. We identified three studies that evaluated the effect of omega-3 FA on the treatment and progression of MS. Among these, one study was an RCT[40] and two were single arm, open-label clinical trials.[62, 63] The RCT assessed the effect of treatment with an omega-3 FA supplement (MaxEPA) on disability and relapse rates (Table 3.7). There were no significant differences in disability or relapse rates between the treatment and placebo groups. Results for disability did not differ on subgroup analyses of patients with disease duration of 5 years or less and baseline Kurtzke disability scores of 2 or less (Table 3.7).

The one-arm open-label studies[62, 63] described the effects of supplementation with omega-3 FA on disability and progression among patients with MS (Table 3.8). Both studies reported a significant reduction on the Expanded Disability Status Scale (EDSS) after treatment with the omega-3 supplement; one also reported improvement on an index of disease progression.[62]

Sub-populations. The effects of omega-3 FA on subpopulations were not assessed.

Covariates. The effects of covariates on omega-3 FA effects were not assessed.

Effects of source, dose, and exposure duration

Source: The source of omega-3 FA was fish oil in one study[63] and fish oil capsules in the other.[62]

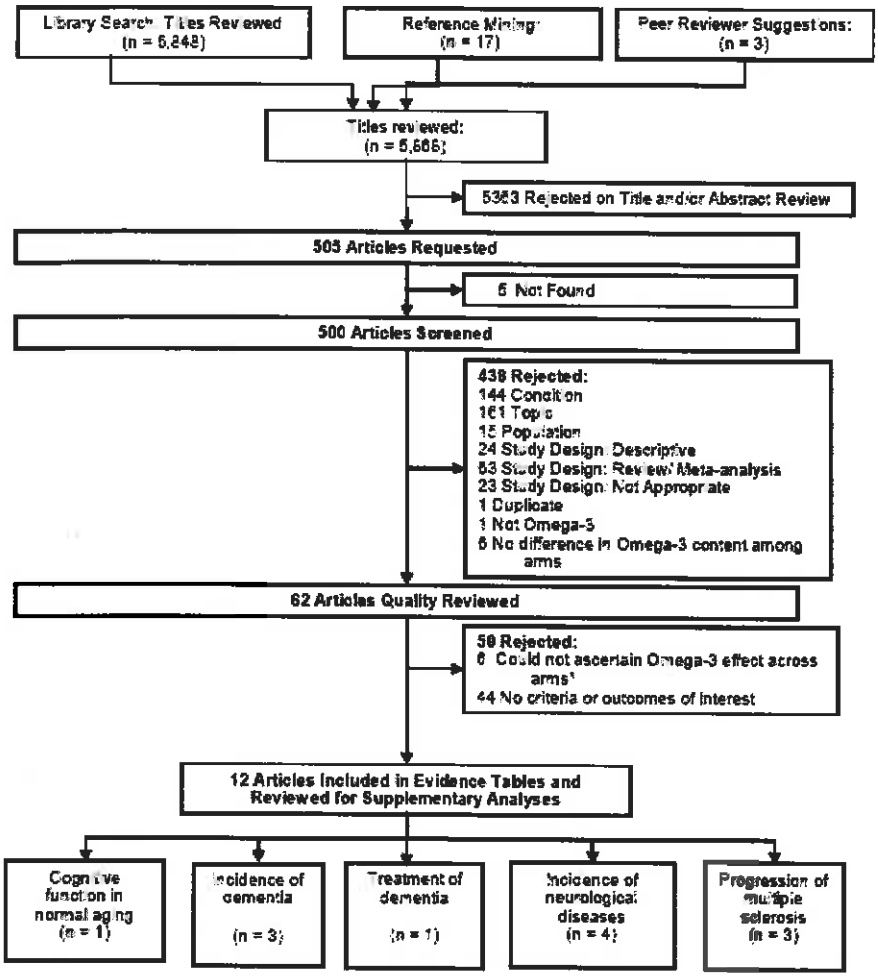
Dose: A single dose was assessed in each study; hence, dose effect was not assessed.

Exposure Duration: The effect of exposure duration was not assessed.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. The RCT[40] had an applicability rating of II-B and a summary quality score of B (Jadad score = 3); concealment of allocation was not reported. This study is applicable to the general population of adult patients with multiple sclerosis (Table 3.9). The two open label one-arm trials[62, 63] were both of poor methodologic quality: there was no comparison group or blinding; additionally there was no description of withdrawals or dropouts. Both of these trials had a Jadad score of 0. The applicability rating of these studies was II-B.

Figures



* Omega-3 effects might not be ascertainable for a variety of reasons, including Omega-3 given in conjunction with another supplement and the effect of Omega-3 not quantified.

Figure 3.1 Literature Flow

Tables

Table 3.1 Risk of cognitive impairment or decline in normal aging reported in a cohort study with consumption of omega-3 fatty acids, by categorization of omega-3 fatty acid intake.

Author, Year	Outcome	Study arm (quartile, quintile or dose group)	n	Amount	Estimates of effect				
Cohort					**Age-adjusted OR (95% CI)**		**Multivariable RR (95% CI)**		**Multivariable Adjustors**
Fish									
Kalmijn, 1997[59]	Cognitive impairment	None	NR	none	1.0		1.0		Age, education, cigarette smoking, alcohol consumption, energy intake, baseline MMSE score.
Zutphen Elderly Study		High	NR	> 0–20 g/day	0.43	(0.23–0.78)	0.63	(0.33–1.21)	
			Total 476			p = 0.004‡		p = 0.13‡	
	Cognitive decline	None	NR	none	NR		1.0		
		High	NR	> 0–20 g/day	NR		0.45	(0.17–1.16)	
			Total 342					p = 0.09‡	
Omega-3 fatty acids†									
Kalmijn, 1997[59]	Cognitive impairment	Low	NR	0–37.5 mg/day	1.00		NR		Age, education, cigarette smoking, alcohol consumption, energy intake, baseline MMSE score.
Zutphen Elderly Study		Medium	NR	37.5–155.5 mg/day	1.09	(0.65–1.80)	NR		
		High	NR	155.5–2,110.5 mg/d	0.96	(0.57–1.62)	NR		
			Total 476			p = 0.9‡			
	Cognitive decline	Low	NR	0–37.5 mg/day	1.00	NR	NR		

Author, Year	Outcome	Study arm (quartile, quintile or dose group)	n	Amount	Estimates of effect		
Cohort					Age-adjusted OR (95% CI)	Multivariable RR (95% CI)	Multivariable Adjustors
		Medium	NR	37.5–155.5 mg/day	0.85 (0.40–1.82)	NR	
		High	NR	155.5–2,110.5 mg/d	0.78 (0.35–1.73)	NR	
		Total	342		p=0.5		

* NR= not reported;

† EPA and DHA:

‡ test for trend.

Table 3.2 Risk of dementia reported in prospective cohort studies for different categories of consumption of omega-3 fatty acids, by category of consumption.*

Author, Year Cohort	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
Cohort						**Age adjusted RR (95% CI)**		**Multivariable adjusted RR (95% CI)**		**Multivariable Adjustors**
FISH										
Barberger-Gateau, 2002[21]	Dementia	1	NR	NR	NR	1.0		1.0		Age, sex, education
PAQUID (Personnes Agées QUID) Study		2	1122	124	At least once a week	0.66†	(0.47–0.93)	0.73†	(0.52–1.03)	
	Alzheimer's disease	1	NR	NR	NR	1.0		NR		
		2	1122	99	At least once a week	0.69†	(0.47–1.01)	NR		
			Total 1122	223						
Kalmijn, 1997[67]	Total dementia	1	1807	58	≤ 3 g/day	NR		1.0		Age, sex, education, total energy intake.
Rotterdam Study		2	1773	58	3.0–18.5 g/day	NR		0.8	(0.4–1.4)	
		3	1806	58	> 18.5 g/day	NR		0.4	(0.2–0.9)	
				58					p = 0.03‡	
	Alzheimer's disease without vascular component	1	1807	37	≤ 3 g/day	NR		1.0		
		2	1773	37	3.0–18.5 g/day	NR		0.9	(0.4–1.8)	
		3	1806	37	> 18.5 g/day	NR		0.3	(0.1–0.9)	

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
Cohort						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
				37					p = 0.005‡	
	Dementia with a vascular component	1	1807	12	≤ 3 g/day	NR		1.0		
		2	1773	12	3.0–18.5 g/day	NR		0.6	(0.2–2.5)	
		3	1806	12	> 18.5 g/day	NR		0.7	(0.2–2.8)	
			Total 5386	12					p = 0.39‡	
Morris, 2003[23]	Alzheimer's disease	1	121	32	never	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε 4 status.
Chicago Health and Aging Project		2	250	39	1–3 servings/ month	0.7	(0.3–1.6)	0.6	(0.3–1.3)	
		3	296	43	1 serving/ week	0.5	(0.2–1.0)	0.4	(0.2–0.9)	
		4	148	26	≥ 2 servings/week	0.6	(0.2–0.9)	0.4	(0.2–0.9)	
			Total 815	140			p = 0.18‡		p = 0.07‡	
Omega-3 fatty acids										

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
Cohort						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
Morris, 2003[23]	Alzheimer's disease	1	NR	32	0.9 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε 4 status.
Chicago Health and Aging Project		2	NR	30	1.13 g/day	1.1	(0.4–2.9)	1.2	(0.5–3.0)	
		3	NR	22	1.30 g/day	0.5	(0.2–1.4)	0.6	(0.2–1.7)	
		4	NR	24	1.49 g/day	0.6	(0.2–1.5)	0.7	(0.3–1.6)	
		5	NR	23	1.75 g/day	0.3	(0.1–0.7)	0.4	(0.1–0.9)	
			Total 815	131			p = 0.01‡		p = 0.01‡	
ALA										
Morris, 2003[23]	Alzheimer's disease	1	NR	26	0.72 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε 4 status.
Chicago Health and Aging Project		2	NR	33	0.92g/day	1.7	(0.7–3.8)	1.8	(0.8–3.8)	
		3	NR	24	1.06g/day	0.8	(0.4–1.9)	0.8	(0.4–2.0)	

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
Cohort						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
		4	NR	25	1.23g/day	0.8	(0.4–1.7)	0.9	(0.4–2.0)	
		5	NR	23	1.46g/day	0.5	(0.2–1.1)	0.7	(0.3–1.6)	
			Total 815	131			p = 0.01‡		p = 0.10‡	
DHA										
Morris, 2003 [23]	Alzheimer's disease	1	NR	28	0.03 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε 4 status.
Chicago Health and Aging Project		2	NR	45	0.05 g/day	0.8	(0.3–2.1)	0.8	(0.3–2.1)	
		3	NR	14	0.06 g/day	0.4	(0.1–1.1)	0.4	(0.1–1.0)	
		4	NR	19	0.07 g/day	0.3	(0.1–0.9)	0.2	(0.1–0.8)	
		5	NR	25	0.10 g/day	0.4	(0.2–1.1)	0.3	(0.1–0.9)	
			Total 815	131			p = 0.05‡		p = 0.02‡	
EPA										

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	No. of Cases	Amount by category	Estimates of effect				
Cohort						Age adjusted RR (95% CI)		Multivariable adjusted RR (95% CI)		Multivariable Adjustors
Morris, 2003 [23]	Alzheimer's disease	1	NR	55	0.0 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε 4 status.
Chicago Health and Aging Project		2	NR	NR§	0.0 g/day	NR§	NR§	NR§	NR§	
		3	NR	35	0.01 g/day	1.0	(0.4–2.4)	1.1	(0.4–2.8)	
		4	NR	14	0.02 g/day	0.5	(0.2–1.2)	0.5	(0.2–1.2)	
		5	NR	27	0.03 g/day	0.9	(0.4–2.1)	0.9	(0.4–2.3)	
			Total 815	131			p = 0.40‡		p = 0.40‡	

* NR = not reported, g = grams;

† hazard ratio;

‡ age and sex adjusted; test for trend;

§ Authors report that 40% of participants had 0 g/day of intake.

Author, Year	Results				

Table 3.3 The effect of omega-3 fatty acids on the treatment of dementia in one randomized controlled trial stratified by outcome.*

Author, Year	Results				
Terano, 1994[24]	Total n	Before	After 3 months	After 6 months	After 12 months
Mean scores of HDS-R					
Standard nursing home diet	10	16.3	16.7	16.7	15.3
Standard nursing home diet PLUS DHA 4.3 grams/day	10	17.2	20.6†	19.9†	20.2
Mean scores of MMSE					
Standard nursing home diet	10	19.7	19.4	19.6†	19.1
Standard nursing home diet PLUS DHA 4.3 grams/day	10	20.1	21.3	22.2	21.9

* HDS-R = Hasegawa's Dementia rating scale;

MMSE = Mini Mental Status Exam;

† $p < 0.05$ for comparisons between groups with paired t-test.

Table 3.4 Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on treatment of dementia in randomized controlled trials (RCTs)

	Methodologic Quality		
Applicability	**A**	**B**	**C**
I			
II			Terano[24]
III			

Table 3.6 Risk of neurological diseases reported in prospective cohort or case-control studies for different categories of consumption of fish, by disease.*

Disease	Author, Year Study Design		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect Multivariable adjusted RR (95% CI)		Multivariable Adjustors, Matching parameters	
Fish									
Multiple sclerosis	Zhang, 2000[61] Cohort Study: The Nurses' Health Study I and II		Dose Groups 1	81	< 1/week	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption *Matching:* NA	
			2	77	1–2.9/week	1.0	(0.8–1.4)		
			3	37	3–4.9/week	0.9	(0.6–1.3)		
									p = 0.79‡
Multiple sclerosis	Ghadirian, 1998,[43] Case control study	Men	Control	64	-	1.0		*Multivariable adjustors:* Total energy, body mass index *Matching:* Age, sex, phone number	
			Case	61	-	1.08§	(0.84–1.40)		
		Women	Control	138	-	1.0			
			Case	136	-	0.83§	(0.69–1.00)		
		All	Control	202	-	1.0			
			Case	197	-	0.91§	(0.78–1.05)		

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					**Multivariable adjusted RR (95% CI)**		**Multivariable Adjustors, Matching parameters**
Cerebral palsy	Petridou, 1998,[60]		Control	166	1/week	1.0		*Multivariable adjustors:* 'Core' variables‖ plus total energy intake, body mass index
	Case control study		Case	58	1/week	0.63	(0.37–1.08)	*Matching:* Age, neighborhood or age, physician
Omega-3 fat from fish								
Parkinson's Disease	Chen, 2003[34]	Men	Quintiles					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
	Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study		1	NR	0.03 % of energy	1.0		*Matching:* NA
			2	NR	0.07% of energy	0.84	(0.52–1.37)	
			3	NR	0.1% of energy	1.08	(0.69–1.69)	
			4	NR	0.2% of energy	0.88	(0.55–1.40)	
			5	NR	0.3 % of energy	0.99	(0.63–1.55)	
				Total 47,331	p = 0.9‡			
		Women	Quintiles					
			1	NR	0.03 % of	1.0		
			2	NR	0.05 % of energy	0.70	(0.41–1.19)	

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					Multivariable adjusted RR (95% CI)		Multivariable Adjustors,
								Matching parameters
			3	NR	0.08 % of energy	0.76	(0.45–1.29)	
			4	NR	0.1% of energy	0.75	(0.45–1.26)	
			5	NR	0.2 % of energy	0.90	(0.55–1.47)	
			Total 88,653				p = 0.9‡	
		Pooled men and women	Quintiles					
			1	NR	NR	1.0		
			2	NR	NR	0.77	(0.54–1.11)	
			3	NR	NR	0.93	(0.66–1.31)	
			4	NR	NR	0.82	(0.58–1.16)	
			5	NR	NR	0.94	(0.68–1.32)	
			Total 135,894				p = 0.9‡	
ALA								
Multiple Sclerosis	Zhang, 2000[61]		Groups					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
	Cohort Study: The Nurses' Health Study I and II		1	NR	< 1% of energy	1.0		*Matching:* NA

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					**Multivariable adjusted RR (95% CI)**		**Multivariable Adjustors,**
								Matching parameters
			2	NR	≥ 1% of energy	0.3	(0.1–1.1)	
Parkinson's Disease	Chen, 2003[34]	Men	Quintiles					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
	Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study		1	NR	0.05 % of energy	1.0		*Matching:* NA
			2	NR	0.06% of energy	0.54	(0.34–0.87)	
			3	NR	0.08% of energy	0.75	(0.49–1.15)	
			4	NR	0.09% of energy	0.88	(0.58–1.32)	
			5	NR	0.1 % of energy	0.69	(0.45–1.07)	
			Total 47,331				p = 0.4‡	
		Women	Quintiles					
			1	NR	0.04 % of energy	1.0		
			2	NR	0.06 % of energy	0.83	(0.51–1.34)	
			3	NR	0.07 % of energy	0.71	(0.43–1.17)	
			4	NR	0.09% of energy	0.68	(0.41–1.13)	

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					Multivariable adjusted RR (95% CI)		Multivariable Adjustors, Matching parameters
			5	NR	0.1 % of energy	0.60	(0.35–1.01)	
			Total 88,563				p = 0.04‡	
		Pooled men and women	Quintiles					
			1	NR	NR	1.0		
			2	NR	NR	0.67	(0.47–0.93)	
			3	NR	NR	0.73	(0.53–1.01)	
			4	NR	NR	0.79	(0.57–1.09)	
			5	NR	NR	0.65	(0.46–0.91)	
			Total 135,894				p = 0.05‡	
EPA								
Parkinson's Disease	Chen, 2003[34]	Men	Quintiles					
	Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study		1	NR	0.009 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
			2	NR	0.02 % of energy	0.77	(0.48–1.25)	

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					Multivariable adjusted RR (95% CI)		Multivariable Adjustors, Matching parameters
			3	NR	0.04 % of energy	0.88	(0.56–1.39)	
			4	NR	0.06 % of energy	0.92	(0.59–1.44)	
			5	NR	0.1 % of energy	0.91	(0.59–1.42)	
			Total 47,331				p = 0.9‡	
		Women	Quintiles					
			1	NR	0.007 % of energy	1.0		
			2	NR	0.01 % of energy	0.67	(0.39–1.16)	
			3	NR	0.02 % of energy	0.80	(0.48–1.34)	
			4	NR	0.04 % of energy	0.74	(0.44–1.24)	
			5	NR	0.07 % of energy	0.91	(0.56–1.49)	
			Total 88,563				p = 0.8‡	
		Pooled men and women	Quintiles					
			1	NR	NR	1.0		

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					Multivariable adjusted RR (95% CI)		Multivariable Adjustors, Matching parameters
			2	NR	NR	0.73	(0.51–1.04)	
			3	NR	NR	0.84	(0.60–1.19)	
			4	NR	NR	0.84	(0.60–1.18)	
			5	NR	NR	0.91	(0.66–1.27)	
			Total 135,894				p = 0.9‡	
DHA								
Parkinson's Disease	Chen, 2003[34]	Men	Quintiles					*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
	Cohort Study: Health Professional Follow-up Study and The Nurses' Health Study		1	NR	0.02 % of energy	1		
			2	NR	0.05 % of energy	0.79	(0.49–1.28)	
			3	NR	0.07 % of energy	1.05	(0.67–1.64)	
			4	NR	0.1 % of energy	0.90	(0.57–1.42)	
			5	NR	0.2 % of energy	0.92	(0.58–1.44)	
			Total 47,331				p = 0.9‡	

Disease	Author, Year		Study arm (quartile; quintile; dose group; case or control)	n†	Amount	Estimates of effect		
	Study Design					Multivariable adjusted RR (95% CI)		Multivariable Adjustors,
								Matching parameters
		Women	Quintiles					
			1	NR	0.02 % of energy	1		
			2	NR	0.04 % of energy	0.62	(0.36–1.07)	
			3	NR	0.06 % of energy	0.65	(0.38–1.09)	
			4	NR	0.08 % of energy	0.81	(0.49–1.32)	
			5	NR	0.1 % of energy	0.76	(0.46–1.26)	
			Total 88,563				p = 0.8‡	
		Pooled men and women	Quintiles					
			1	NR	NR	1		
			2	NR	NR	0.71	(0.49–1.02)	
			3	NR	NR	0.86	(0.61–1.21)	
			4	NR	NR	0.86	(0.61–1.20)	
			5	NR	NR	0.84	(0.60–1.18)	
			Total 135,894				p = 0.8‡	

* NR = Not Reported;

† Number of people included in analysis;

‡ test for trend.

|| Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of iron during pregnancy, intentional physical exercise during pregnancy, painless delivery classes;

§ Risk of MS per 100 grams of fish per day (log transformation).

Parameters	Chen, 2003	Ghadirian, 1998	Petridou, 1998	Zhang, 2000

Table 3.5 Parameters of methodological quality.*

Parameters	Chen, 2003[34]	Ghadirian, 1998[43]	Petridou, 1998[60]	Zhang, 2000[61]
Adjustment for confounders	Y	Y	Y	Y
Blinding of exposure/outcome	Y	Y	Y	Y
Valid ascertainment of outcome	Y	Y	Y	Y
Valid ascertainment of exposure	Y	Y	Y	Y
Exposure before outcome	Y	Y	Y	Y
Selection bias	N	N	Y	N
Description of withdrawals and dropouts	NR	Y	Y	Y

* NR = not reported.

Author, Year Treatment Group Disability, number (%)of patients Mean relapse rates

Table 3.7 The effect of omega-3 fatty acids on progression of multiple sclerosis reported in one randomized controlled trial (RCT).*

Author, Year	Treatment Group	Disability, number (%)of patients						Mean relapse rates			
Bates, 1989[40]		Overall		Kurtzke ≤ 2		Duration ≤ 5 years		Kurtzke ≤ 2		Kurtzke > 2	
		Better/same	Worse	Better/same	Worse	Better/same	Worse	Better/same	Worse	Better/same	Worse
	Max EPA 10 grams/day for 24 months	79 (51)	66 (43)	50 (59)	35 (41)	30 (57)	23 (43)	0.44	0.15	0.55	0.05
	Olive oil 10 grams/day for 24 months	65 (42)	82 (52)	41 (46)	49 (54)	24 (42)	33 (58)	0.55	0.16	0.63	0.70

* No significant difference between groups for any comparisons.

Table 3.8 The effect of omega-3 fatty acids on progression of multiple sclerosis in open-label trials stratified by outcome

Author, Year	Intervention	Mean EDSS Scores*		Mean Progression Index	
		n, clinical diagnosis	Before	After	Before	After
Cendrowski, 1986[62]	MaxEPA (4.2 g/day EPA; 2.8 g/day DHA)	5, acute remitting MS	3.30	2.70	0.59	0.44†
Cendrowski, 1986[62]	MaxEPA (4.2 g/day EPA; 2.8 g/day DHA)	7; slowly progressive MS	6.92	7.07	0.35	0.36
Nordvik, 2000[63]	Fish oil supplement (0.4 g/day EPA; 05 g/day DHA)	16; MS	2.16	1.63‡	NA	NA

NA = Not Applicable;

* EDSS = Expanded Disability Status Scale;

† $p < 0.05$;

‡ = $p = 0.005$.

Methodologic Quality

Table 3.9 Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on progression of multiple sclerosis in randomized controlled trials (RCTs)

Applicability	Methodologic Quality A	B	C
I			
II		Bates[40]	
III			

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

4 Discussion

Overview

We screened 5,868 titles, from which we reviewed 500 full-text articles. Among these, 62 articles met our inclusion criteria for further review. Fifty were rejected and 12 met our inclusion criteria and were reviewed further for data abstraction. Among these, two articles were randomized controlled trials, six articles were prospective cohort studies, two articles were case-controls, and two were one-arm open label trials.

Main Findings

Effects of omega-3 fatty acids

Cognitive function in normal aging. In a single prospective cohort study[59] that evaluated the effects of omega-3 fatty acid on cognitive function in normal aging, there was no significant association between omega-3 FA intake in the form of fish consumption and cognitive decline.

Incidence of dementia. Among three prospective cohort studies[21, 23, 67] that assessed the effects of omega-3 FA on the incidence of dementia, fish consumption was associated with a statistically and clinically significant reduction in the incidence of non-Alzheimer's dementia in all three.[67] Fish consumption was associated with a reduced risk of Alzheimer's dementia in all three of the studies; the association was statistically significant in one[67] and nearly so in the other two[21, 23] (Table 3.2). Total omega-3 FA consumption and consumption of DHA were associated with a significant reduction in the incidence of Alzheimer's disease for the general population; consumption of ALA and EPA were not.[23] Among individuals who were APOE-4 positive, ALA was associated with a reduced risk.

Treatment of dementia. One RCT[24] assessed omega-3 fatty acids as a treatment for dementia. This study demonstrated statistically significant improvements on both Hasegawa's Dementia rating scale and the MMSE scores with omega-3 supplementation. However, the sample size was small and the methodologic quality was poor.

Incidence of neurological diseases. We identified four studies that assessed the association of omega-3 FA consumption with risk or incidence of particular neurological diseases other than dementia: two assessed the incidence of MS,[43, 61] one assessed the risk of Parkinson's disease,[34] and one assessed the risk of cerebral palsy.[60] Overall, there was no significant association between omega-3 FA and the incidence of MS in either a study that pooled data across two cohort studies[61] or in a case-control study.[43] However, the case-control study did demonstrate a reduced risk of MS with fish consumption, but only among women. A single observational cohort study[34] found that ALA was associated with a reduced risk of Parkinson's disease when comparing highest and lowest quintile of intake in a pooled analysis of men and women; among women, but not men, there was a trend for risk reduction. There was no significant association between dietary intake of other omega-3 FAs and Parkinson's disease. A single case-control study[60] found a reduced risk of cerebral palsy in offspring of women who consumed fish at least once a week throughout pregnancy, relative to women who did not.

Progression of multiple sclerosis. We identified one RCT[40] and two single arm, open-label clinical trials[62, 63] that assessed the effect of omega-3 fatty acids on the progression of MS.[63–66] There were no significant differences in disability or relapse rates between the treatment and placebo groups in the RCT.[40] The one-arm open label trials both

reported a significant reduction on the Expanded Disability Status Scale (EDSS) after treatment with the omega-3 supplement; one also reported improvement on an index of disease progression.[62]

Dose, source, duration effects and sustainment of effect. Data were insufficient to draw conclusions about source or duration effects or about sustainment of effect.

Quality and applicability. The quality of the clinical trials was generally poor. Among the two RCTs that met our inclusion criteria, one[33] was of good quality with an overall summary quality of B (Jadad score 3, no concealment of allocation), and the other[24] was of poor quality with an overall summary quality of C (Jadad score1, no concealment of allocation). The two open-label one-arm trials[62, 63] were both of poor methodologic quality: there was no comparison group or blinding; additionally there was no description of withdrawals or dropouts. The applicability ratings for all four of these clinical trials were II, meaning that the study populations were representative of a subgroup of the general population; these subjects had either MS or dementia.

The quality of the eight observational studies was generally good. Among these six prospective observational cohort and two case-control studies, all eight adjusted for confounders, reported using valid methods to ascertain outcomes, and confirmed that the exposure occurred prior to the outcome. The methods used to enroll subjects in one study would be expected to introduce selection bias.[60] All but one study described withdrawals and dropouts[34] or a valid method to ascertain dietary intake[21] (method used was not described). Only three of the studies explicitly described whether the investigators were blinded to information on exposure when obtaining data on outcome or on outcome when obtaining data on exposure.[23, 34, 61] For the two case-control studies, we also assessed whether the case and control groups were comparable, and they were in both studies.[43, 60] The applicability ratings were I (representative of the US population) for one study[23] and II for all other studies. The studies with applicability ratings of II either had subjects that were part of a subpopulation[34, 43, 60, 61] and/ or were population-based, but the populations were not from the United States.[21, 59, 67]

Limitations

It is important to point out that a major limitation of studies of omega-3 FA and disease is the lack of standardized methods to measure nutrient intakes.[68] Thus, it is possible to overestimate or underestimate true associations with outcomes, because of errors in measurement of nutrients.

Furthermore, the studies we reviewed lacked a uniform or consistent approach to quantifying the type of omega-3 FA. For example, some measured nutrient intake from food frequency questionnaires without reporting type of fish or method of preparation; other studies defined omega-3 fatty acid supplements. This issue will increasingly become important in the design of future studies of omega-3 fatty acids and disease.

Another major limitation with respect to studies relating omega-3 FA interventions to dementia, particularly Alzheimer's disease, is that the majority of studies have been done in subjects aged 60 and older. Since the length of the latency period for AD is unknown and may precede the presentation of any symptoms by several decades, the potential effect of implementing dietary interventions aimed at prevention at an advanced age may be limited. Furthermore, in studies that assessed the effects of omega-3 fatty acids on cognitive function in normal aging or dementia, standard measures often are not used or the instruments used to assess cognitive function lack uniformity.

It is also important to note that in observational studies, it is not possible to control exposure,[69] which can lead to confounding.[70]

An additional limitation is the possibility of publication bias. For large observational studies, this issue is slightly different than that observed for randomized trials. Publication bias for the latter generally means that no results of the trial are published at all. For the former, which are the main source of evidence for this report, findings may be published, but only for outcomes that achieve statistical significance, with no regard for whether such outcomes were secondary in nature. Results for primary outcomes may not be published. We must interpret our findings in light of such possible publication bias

It is possible that additional information that would change our conclusions is available in reports that we were unable to locate or for which we were unable to find a translator. However, among 505 requested articles, only five were not found, and we were able to screen all 500 articles retrieved.

Conclusions

For each of the conditions assessed in this report, conclusions can be drawn from a few studies on the effects of Omega-3 FA. Additionally, the strength of evidence for effects of omega-3 FA on outcomes in the conditions assessed varies greatly. The evidence suggests a possible association between omega- 3 FA and reduced risk of dementia. However, due to the small number of studies that inform this topic, further research is necessary before a strong conclusion can be drawn. Data are insufficient to draw conclusions about the effects of omega-3 FA on incidence of Parkinson's disease, cerebral palsy, or MS. In addition, the evidence regarding the progression of MS is inconsistent and inconclusive. There was insufficient evidence in the studies that met our systematic inclusion criteria to draw any substantive conclusions on omega-3 fatty acid intake. The paucity of evidence in this area suggests that further epidemiological and clinical research remains to be done before any conclusions can be drawn or policy recommendations can be made in this area.

Future Research

We offer the following observations and recommendations regarding future research on the effects of omega-3 FA on the various neurological conditions reviewed.

1. Additional research on the effects of omega-3 FA needs to be performed on all of the conditions reviewed in this report before recommendations regarding the use of omega-3 FA can be made for these conditions.
2. Of particular importance, properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g. three to five years of follow-up) need to be conducted for dementia, especially Alzheimer's disease, as distinct from vascular dementia.
3. Given the concern described above regarding the possible difficulty of conducting valid studies on dementia, due to a lengthy presymptomatic latency period, it would be of interest to conduct intervention clinical trials of omega-3 fatty acids in middle-aged adults as well as in populations of cognitively-impaired adults prior to a dementia diagnosis, such as individuals with various sub-types of mild cognitive impairment (MCI).
4. Properly designed randomized clinical trials that are sufficiently powered and of an adequate length (e.g. three to five years of follow-up) need to be conducted for multiple sclerosis.
5. Studies should address the effects of different types of omega-3 fatty acids (i.e. DHA, EPA, ALA, and total omega-3 FA) as well as the ratio of omega-3 to omega-6 FA.
6. Studies that assess the effects of omega-3 FA should be designed to evaluate the effect of source, dose, treatment duration, and the sustainment of effect after discontinuation of omega-3 FA consumption.
7. Trials of omega-3 FA should include a baseline assessment of dietary omega-3 and omega-6 FA intake.
8. In controlled trials that assess the effects of omega-3 FA, analysis should include and report explicit testing of the effects of the omega-3 FA relative to the control substance.
9. All studies that assess the effects of omega-3 FA should use standard validated instruments to assess clinical outcomes.
10. Studies that investigate the effects of omega-3 FA on cognition should include repeated measures of cognitive function using standard validated instruments to evaluate within-person cognitive change.
11. All studies that assess the effects of omega-3 FA should use standard validated dietary assessment instruments to assess nutritional intake.
12. Observational studies should report data about type of fish consumed and method of preparation.

13. Observational studies focused on repeated measures of diet for long-term intake, and sub-group analysis among persons with cardiovascular conditions (including history of stroke or myocardial infarction) also need to be performed in order to determine whether change in diet among these sub-groups results is confounding.

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

Acronyms

AA	Arachidonic acid	Mo	Month
Ab	Antibody	MS	Multiple sclerosis
AHRQ	Agency for Healthcare Research and Quality	n	Number
AI	Adequate intake	n-3	Omega-3
ALA	Alpha-linolenic acid	n-6	Omega-6
AMDR	Acceptable macronutrient distribution ranges	NA	Not applicable
ANCOVA	Analysis of covariance	NHANES III	The Third National Health and Nutrition Examination
ANOVA	Analysis of variance	NCI	National Cancer Institute
Ca	Calcium	NEI	National Eye Institute
CCT	Controlled clinical trial	NEMC	New England Medical Center
CI	Confidence interval	NHANES	National Health and Nutrition Examination
CP	Cerebral palsy	NHLBI	National Heart, Lung and Blood Institute
CRP	C-reactive protein	NIAAA	National Institute of Alcohol Abuse and Alcoholism
CSFII	Continuing Food Survey of Intakes by Individuals	NIAID	National Institute of Allergy and Infectious Diseases
d	day	NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
D6D	Delta-6 Desaturase	NICHD	National Institute of Child Health and Human Development
DGLA	Dihomo-gamma-linolenic acid	NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
DHA	Docosahexaenoic acid	NIH	National Institutes of Health
DPA	Docosapentaenoic acid	NINCDS Criteria	National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Criteria
DRI	Dietary Reference Intake	NNH	Number needed to harm
Ds-DNA	Double-stranded DNA	NR	Not reported

EDSS	Expanded Disability Status Scale	ODS	Office of Dietary Supplements
EF	Effect size	PG	Prostaglandin
EFA	Essential fatty acid	PGD	Prostaglandin-D
EPA	Eicosapentaenoic acid	PGE	Prostaglandin-E
EPC	Evidence-Based Practice Center	PGF	Prostaglandin-F
ESR	Erythrocyte sedimentation rate	PGL	Prostaglandin-L
FNB	Food and Nutrition Board	PGH	Prostaglandin-H
FFQ	Food Frequency Questionnaire	PUFA	Polyunsaturated fatty acid
g	Grams	QRF	Quality review form
GLA	Gamma-linolenic acid	RCT	Randomized controlled trial
HDL	High density lipoprotein	RDA	Recommended daily allowances
		RXT	Randomized crossover trial
IL-1β	Interleukin 1β	Sd	Standard deviation
IOM	Institute of Medicine	SCEPC	Southern California Evidence-Based Practice Center
LA	Linoleic acid	SEM	Standard errors of the means
LC PUFA	Long-chain polyunsaturated fatty acid	TEP	Technical expert panel
LDL	Low density lipoprotein	TNF-*a*	Tumor necrosis factor-*a*
MA	Metaanalysis	TX	Treatment
MANOVA	Multivariable analysis of variance	TXA	Thromboxane-A
MeSH Term	Medical Subject Headings Term	UCLA	University of California, Los Angeles
mg/dl	Milligrams per deciliter	VLCFA	Very long chain fatty acid
min	Minutes	VLN-3FA	Very long chain n-3 fatty acids
		Wk	Week

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

Appendixes

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Appendix A. Methologic Approach

Preliminary Research Questions

Table A.1.1 Preliminary research questions

GENERAL QUESTIONS: Questions posed for all three participating EPCs, for years 1 and 2.

1. What is the evidence that variable clinical effects may reflect differences in:

   • Serving size (fish vs. dietary supplement);

   • Source (fish, food, plant) vs. dietary supplement (fish oil, plant oil);

   • Specific type(s) of omega-3 fatty acids (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA), fish, fish oil), or the ratio of omega-6/omega-3 fatty acids used;

   • Manufacturer (different purity, presence of other potentially active agents)?

2. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acids (DHA, EPA, DPA, ALA, fish oil, fish)?

3. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations such as diabetics?

4. What are the mean and median intakes of DHA, EPA, DPA, ALA, fish, fish oil, omega-6, omega-6/omega-3 ratio in the US population?

5. What is the evidence that omega-3 fatty acids influence overall energy balance?

6. What is the evidence that accurate interpretation of the results of clinical studies is dependent on knowing the absolute fatty acid content of the baseline data, the relative fatty acid content of the baseline diet, or the tissue ratios of fatty acids (omega-6/omega-3) during the investigative period?

DISEASE-SPECIFIC QUESTIONS: questions posed to the SCEPC for Year 2 of the project:

Neurology:

1. What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function with aging?

2. What is the evidence that the level of brain or retinal DHA levels affect the incidence of neurological diseases?

Technical Expert Panel

The members of our technical expert panel are listed in Table A.2.1.. We conducted our TEP meetings via teleconference on December 18, 2003. Dr. Beth Collins-Sharp, the Task Order Officer, and Jacqueline Besteman, Director of the Evidence-Based Practice Center Program, represented AHRQ on these calls; Dr. Anne Thurn, Director of the Evidence-Based Review Program, represented ODS; and Dr. Catherine MacLean, the Task Order Director, and Rena Hasenfeld, the Project Manager, represented the SCEPC. The key comments and recommendations of the TEP are summarized in Table A.2.2. The TEP continued to advise the SCEPC throughout the project via mail, fax, e-mail, and phone calls.

Table A.2.1 Technical expert panel members

Neurology

Name	Area of Expertise	Institution
Alberto Ascherio, M.D., M.P.H., Dr. P.H.	Neurology	Harvard Medical School
Julie Conquer, M.S., Ph.D.	Neurological Disorders/Nutrition	University of Guelph
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Irwin Rosenberg, M.D.	Nutrition/Aging	Tufts University
Paul Sheehy, Ph.D.	Neurology	National Institute of Neurological Disorders and Stroke
Molly Wagster, Ph.D.	Neurology/Aging	Neuroscience and Neuropsychology of Aging Program

Table A.2.2 Key TEP comments and recommendations

Neurology

1. What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function with aging?

• This question pertains to 1) both maintenance and gains in cognitive functioning with normal aging, and 2) the prevention of dementia..

• The literature primarily includes studies on Alzheimers' disease, but other forms of dementia are also of interest.

• Normative data should be used to measure cognitive function.

• Focus on domains of cognitive function rather than specific tests. Domains of function include 1) general memory, 2) working memory, and 3) executive function.

• Part B of the Trail Making Test and praxis components of the ADAS-Cog are scales that can be used to define normal cognitive function.

• The following instruments can be used to screen for or assess cognitive function in dementia: the Folstein Mini Mental Status Exam, the Alzheimer's Disease Assessment Scale, the Modified Mini-Mental State Examination, and the Telephone Interview of Cognitive Status.

• Look at cognitive domains that are likely to change with aging: executive function, concentration, perceptual/motor processing, verbal learning and memory, verbal and spatial working memory and semantic memory.

• There is no single answer regarding the time frame within which an improvement or decline in cognitive function would occur. Most studies range from 6 months to 1–2 years. To determine the impact of a treatment, you would need to look at the impact over a period of years.

• To determine an effect over time, it may be necessary to look at large observational studies.

• There is more likely to be data on decline over time than on improvement.

• For mild cognitive impairment where there is a significant problem with memory only, look for a change in the conversion rate and at historical cohort studies.

Name Affiliation

look at whether omega-3 fatty acids are both preventing and staving the course of dementia.

• A new set of measurements was published two years ago to assess the rate of change. Do not restrict to these criteria, however, since all of the data should be examined.

• The minimum age limit to assess cognitive function with aging should be 50 years. Other neurological diseases have earlier onset so the age limit should be 45 years for those diseases.

2. What is the evidence that the level of brain or retinal DHA levels affect the incidence of neurological diseases?

• Do not restrict the review to studies that assess brain or retinal levels of DHA.

• Look at brain levels separate from blood levels

• This question is marginal compared to Question #1 and could be limited.

• The mechanisms that affect DHA levels are unknown.

• It would be helpful to have data on blood levels to show the link between dietary intake of omega-3 fatty acids and blood levels.

• If a study doesn't report blood levels, it should not be included.

• The accuracy of dietary intake data is not as effective as blood levels, but dietary intake studies should not be excluded.

• It is critical to include information on studies that have negative results.

• For studies that compare supplements versus placebo, it is important to get information on dose effect.

• The evidence available for dementia is disproportionate to other neurological diseases. Other diseases to consider include Attention Deficit Disorder and non-verbal learning disabilities.

• This question is not necessarily restricted to adults.

• Focus on the effects of omega-3 fatty acids on disease incidence rather than on the effects of omega-3 fatty acids on prevalent disease, except for multiple sclerosis. For multiple sclerosis, the effects of omega-3 fatty acids is of interest.

• Revise the key questions as follows:

  o What is the evidence that omega-3 fatty acids play a role in maintaining cognitive function in normal aging?

  o What is the evidence that omega-3 fatty acids affect the incidence of dementia including Alzheimer's disease?

  o What is the evidence that omega-3 fatty acids are effective in the treatment of dementia including Alzheimer's disease?

  o What is the evidence that omega-3 fatty acids affect the incidence of neurological diseases?

  o What is the evidence that omega-3 fatty acids prevent the progression of multiple sclerosis?

Industry Experts

Table A.3.1 Industry experts that were contacted for data about efficacy of omega-3 fatty acids

Name	Affiliation
Ian Newton	Roche Vitamins

Name	Affiliation
Herb Woolf, PhD	BASF Corporation
Annette Dickinson	Council for Responsible Nutrition

Figure A.3.1 Letter sent to industry experts

Date

Name
Address
City, State. Zip Code

Dear XXX.

I am writing on behalf of the Evidence Based Practice Centers at RAND, New England Medical Center and the University of Ottawa. We are conducting a systematic review of the efficacy and toxicity of omega-3 fatty acids in the prevention and treatment of a number of different diseases/conditions. This review is being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ).

We are contacting you to see if there is any evidence, including unpublished evidence, that you want considered. Our focus is on clinical trials of omega-3 fatty acids in humans, so animal and chemical studies are not necessary.

The specific questions that all the EPCs will address are detailed in the attachment to this letter.

Please contact me with any information that you might have.

Best regards,

Catherine MacLean, M.D., Ph.D.
RAND
1700 Main Street, M 23-C
Santa Monica, CA 90407-2138
Voice: 310 393-0411, x6364
Fax: 310-451-6930

Search Strategies

Table A.4.1 Core search strategy

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.

8. eicosapenta?noic.tw,hw,rw.

Neurology

9. alpha linolenic.tw,hw,rw.

10. (linolenate or cervonic or timnodonic).tw,hw,rw.

11. menhaden oil$.tw,hw,rw.

12. (mediterranean adj diet$).tw.

13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.

14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.

15. (fish adj2 oil$).tw.

16. (cod liver oil$ or marine oil$ or marine fat$).tw.

17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.

18. (fish consumption or fish intake or (fish adj2 diet$)).tw.

19. diet$ fatty acid$.tw.

20. or/1–19

21. dietary fats/

22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.

23. random$.tw.

24. exp clinical trials/ or evaluation studies/

25. follow-up studies/ or prospective studies/

26. or/22–25

27. 21 and 26

28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.

29. (omega 3 or n 3).mp.

30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.

31. 29 and 30

32. 20 or 27 or 28 or 31

Table A.4.2 Literature searches by disease category

Neurology

1. exp fatty acids, omega-3/

2. fatty acids, essential/

3. Dietary Fats, Unsaturated/

4. linolenic acids/

5. exp fish oils/

6. (n 3 fatty acid$ or omega 3).tw.

7. docosahexa?noic.tw,hw,rw.

8. eicosapenta?noic.tw,hw,rw.

9. alpha linolenic.tw,hw,rw.

Neurology

10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1–19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22–25
27. 21 and 26
28. exp Aging/
29. Aged/
30. (aging or aged or geriatric$).tw.
31. or/28–30
32. 27 and 31
33. limit 27 to "all aged <65 and over>"
34. 32 or 33
35. exp Nervous System Diseases/
36. Alzheimer Disease/
37. exp Dementia/
38. parkinson disease/ or Parkinson disease, secondary/
39. parkinson disease/ or Parkinson disease, secondary/
40. exp Multiple Sclerosis/
41. exp Guillain-Barre Syndrome/
42. (alzheimer or parkinson or dementia or multiple sclerosis or guillain barre).tw.
43. (neurological disease$ or neurological disorder$).tw.
44. (neurological disease$ or neurological disorder$).tw.
45. exp Optic Nerve Diseases/

Neurology

46. (myopathy or neuropathy).tw.
47. Cognition Disorders/
48. exp Cognition/
49. (cognition or cognitive).tw.
50. or/35–49
51. 27 and 50
52. exp fatty acids, omega-3/
53. fatty acids, essential/
54. Dietary Fats, Unsaturated/
55. linolenic acids/
56. exp fish oils/
57. (n 3 fatty acid$ or omega 3).tw.
58. docosahexa?noic.tw,hw,rw.
59. eicosapenta?noic.tw,hw,rw.
60. alpha linolenic.tw,hw,rw.
61. (linolenate or cervonic or timnodonic).tw,hw,rw.
62. menhaden oil$.tw,hw,rw.
63. (mediterranean adj diet$).tw.
64. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
65. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
66. (fish adj2 oil$).tw.
67. (cod liver oil$ or marine oil$ or marine fat$).tw.
68. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
69. (fish consumption or fish intake or (fish adj2 diet$)).tw.
70. diet$ fatty acid$.tw.
71. or/52–70
72. dietary fats/
73. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
74. random$.tw.
75. exp clinical trials/ or evaluation studies/
76. follow-up studies/ or prospective studies/
77. or/73–76
78. 72 and 77
79. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
80. (omega 3 or n 3).mp.
81. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.

Neurology Score	Jadad Score	Concealment of Allocation

Applicability **Health state**

82. 80 and 81

83. 71 or 78 or 79 or 82

84. 83 and 50

85. 84 not 51

86. 83 and 31

87. 86 not 34

88. limit 87 to "all aged <65 and over>"

Inclusion/Exclusion Criteria

Table A.5.1 Inclusion/Exclusion Criteria at Screening Stage for Neurology.*

Assessed the effect of omega-3 fatty acids on neurology

Presented research on human subjects

Reported the results of randomized or controlled clinical trials or controlled clinical trials or case-control trials or case series or prospective cohort studies†

Exclusion criteria: cross-sectional studies, case reports

* Language was not a barrier to inclusion;

† We defined a randomized controlled trial (RCT) as one in which the participants were assigned to one of two (or more) study groups using a process of random allocation (e.g., random number generation, coin flips); we defined a controlled clinical trial (CCT) as one in which participants were either: (1) assigned to one of two (or more) study groups using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier), or (2) possibly assigned to one of two (or more) study groups using a process of random or quasi-random allocation.

Evidence Grading System

Table A.6.1 Summary Score for Methodologic Quality

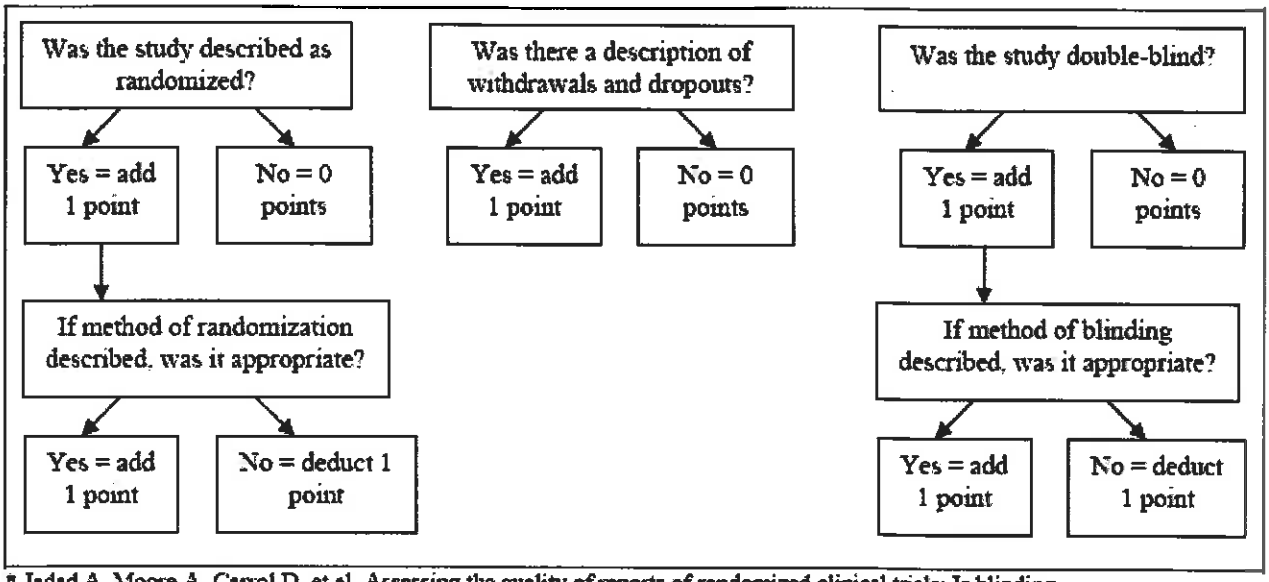
Summary Score	Jadad Score	Concealment of Allocation
A	5	Performed
B	5	Not performed, or Not reported
	3 or 4	Performed, Not performed, or Not reported
	0,1, or 2	Performed
C	0, 1, or 2	Not performed or not reported

Even though a study may focus on a specific target population, limited study size, eligibility criteria and patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To capture this parameter, we categorize studies into the applicability scale described in Table A.6.1.

Table A.6.2 Applicability ratings

Applicability	Area of Expertise	Health state
I Sample is representative of the U.S. population.		A General population. Typical healthy people similar to Americans without known neurological diseases/conditions.
II Sample is representative of a relevant sub-group of the target population, but not the entire population. For example, a study that is restricted to women or a fish oil study in Japan where the background diet is very different from that of the US would fall into this category.		B Diseased population. Subjects with neurological disease/condition.
III Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups. For example, a study of oldest old men or a study of a population on highly controlled diet.		

Figure A.6.1 Jadad score of methodologic quality.*



* Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17:1-12.

External Peer Reviewers

Table A.7.1 Peer Reviewers

Peer Reviewer	Area of Expertise	Affiliation
Judith Ashley, Ph.D., M.S.P.H., R.D.	Nutrition	University of Nevada, Reno
Mona Baumgarten, Ph.D.	Epidemiology	University of Maryland
Graham Colditz, M.D., DR.P.H.	Neurology	Harvard
David Heber, M.D., Ph.D.	Nutrition	UCLA
Martha Clare Morris, Sc.D.	Neurology	Rush Institute for Healthy Aging
Lon Schneider, M.D.	Geriatric Psychiatry/Clinical Neuroscience	University of Southern California

Peer Reviewer	Area of Expertise	Affiliation
Philip A. Wolf, M.D.	Neurology	Boston University
Christina Wolfson Ph.D.	Neurology	McGill University

Bookshelf ID: NBK37646

MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

Appendix B. Coding/Data Abstraction Forms

B.1 Literature Screener Form

Article ID

Reviewers: Assigned on:

2. **Author:**
Title:
Cite:

3. Reviewer: _____

4. Research Topic (circle one)
Omega-3 or synonymous topic ... 1
Unclear, no English abstract ... 8
(If unclear, skip to question 10 on language)
None of the above ... 9 (STOP)

5. Condition(s) Subject(s) studied: (check all that apply)
- Cancer ...
- Cognitive function (e.g., ...)
- Neurological disease ...

None of the above ... (STOP)

6. Study population (check all that apply)
Human ...
Animal ... (STOP)
Unclear ... (STOP)
Other ... (STOP)

7. Study design: (circle one)
Descriptive (historical, editorial, etc.) ... 1 (STOP)
Review meta-analysis ... 2 (STOP)
Randomized clinical trial ... 3
Controlled clinical trial (quasi-randomization) ... 4
Non-randomized clinical trial ... 5
Cohort Case control ... 6
Case series (_ ID) ... 7
Case report (_ ID) ... 8 (STOP)
Other (specify _____) ... 9 (STOP)

8. Type of disease (check all that apply)
CANCER:
Skin ...
Oral cavity and pharynx ...
Colorectal ...
Other gastrointestinal ...
Lung and bronchus ...
Other respiratory ...
Bone and soft tissue ...
Breast ...
Female genital ...
Urinary system ...
Lymphoma ...
Leukemia ...
Preancerous ...
Other cancer ...

NEURO: (check all that apply)
Amyotrophic lateral sclerosis (ALS) ...
Dementia: Alzheimer's Disease ...
Dementia: Multi-Infarct ...
Dementia: Vascular ...
Dementia: NOS ...
Epilepsy ...
Guillain-Barre Syndrome ...
Huntington's Disease ...
Multiple sclerosis ...
Neuromyelitis optica (Devic's syndrome) ...
Optic Neuritis ...
Parkinson's Disease ...
Peroxisomal Biogenesis Disorders Leukodystrophies ...
(Zellweger Syndrome, Metachromatic Leukodystrophy, Alexander Disease, Infantile Refsum Disease)
Other neuro ...

9. Does the study describe the effects of Omega-3 FA on
CANCER:
Cancer incidence ...
Tumor growth ...
Tumor differentiation ...
Apoptosis ...
Chemotherapy ...
Mortality Survival ...
Other cancer outcomes ...
NEURO:
Incidence of neuro disease ...
Outcomes of neuro disease ...
Cognitive function ...
NONE OF THE ABOVE ...

10. Language of article (circle one)
English ... 1
German ... 2
French ... 3
Italian ... 4
Danish ... 5
Russian ... 6
Spanish ... 7
Other (specify _____) ... 8

11. Do you think this article might be a duplicate or include the same data as another study?
No ... 1
Yes ... 2
If yes, which one(s)?
(enter article ID, author, or 9999 for "don't know.")

12. Is there a reference that needs to be checked?
No ... 1
Yes ... 2
If yes, which one(s)?
(enter article ID, author, or 9999 for "don't know.")

Notes:

B.2 Quality Review Form

Article ID_____ Reviewer:

First Author:

(Last Name Only)

Study Number: of Description:

(Leave Blank if only one) (if more than one study)

1 Design: (CIRCLE ONE)

RCT 1
RXT 2
CCT 3
Cohort 4
Case control (STOP if Cancer) 5
Case series ≥ 10 (STOP if Cancer) 6
Other design ..... 7 (STOP)

2 Is there a difference in Omega-3 content between arms (CIRCLE ONE)

Yes 1
Not applicable (Case control & case series) 2
No ..... 3 (STOP)
Unclear ..... 8 (STOP)

3 Is Omega-3 measured in any of the following ways? (CIRCLE ONE)

Diet 1
Tissue 2
Diet and Tissue 3
None of the above 4

4 If the study reports on cognitive function, is the age of the population 45 or older? (CIRCLE ONE)

Yes 1
Study not on cognitive function 2
No ..... 3 (STOP)
Unclear ..... 8 (STOP)

IF THE STUDY DESIGN IS COHORT, CASE CONTROL, OR CASE SERIES PLEASE SKIP TO QUESTION 12.

5. Is the study described as randomized? (CIRCLE ONE)
   Yes 1
   No 2

6. If the study was randomized, was method of randomization appropriate? (CIRCLE ONE)
   Yes 1
   No 2
   Method not described 8
   Not applicable (not randomized) 9

7. Is the study described as (CIRCLE ONE)
   Double blind 1
   Single blind, patient 2
   Single blind, outcome assessment 3
   Open 4
   Blinding not described 8
   Not applicable 9

8. If reported, was the method of double blinding appropriate? (CIRCLE ONE)
   Yes 1
   No 2
   Double blinding method not described 8
   Not applicable 9

9. If study was randomized, did the method of randomization provide for concealment of allocation? (CIRCLE ONE)
   Yes 1
   No 2
   Concealment not described 8
   Not applicable (not randomized) 9

10. Are withdrawals (W) and dropouts (D) described? (CHECK ONE)
    - Yes, reason described for **all** W and D 1
    - Yes, reason described for **some** W and D 2
    - Not described 8
    - Not applicable 9

11. If the design is crossover, please note the duration of the following periods:

Please enter the number and code in the appropriate box.

Period	Number	Unit	Units
X-Over			1. Hour 2. Day 3. Week 4. Month 5. Year 8. ND 9. NA
Run-In			
Wash-Out			

12. Does the study population represent any of the following characteristics? (CHECK ALL THAT APPLY)

	Healthy	Diseased
Typical people	☐	☐
Atypical people (in terms of diet, SES, other factors)	☐	☐
Narrow, atypical people (including highly controlled diet)	☐	☐
Cannot categorize (incomplete data)	☐	☐

13. What was the study's funding source? (CHECK ALL THAT APPLY)
    - Government ☐
    - Hospital ☐
    - Industry ☐
    - Private (non-industry) ☐
    - Unclear ☐
    - Not described ☐

    Other (code(s): _____) ☐

14. What was the number of sites involved in the study? (Enter number or 99 if not reported)

15. In what country was the study conducted? (CHECK ALL THAT APPLY)
    - Australia ☐
    - Denmark ☐
    - Germany ☐
    - Italy ☐
    - Japan ☐
    - Netherlands ☐
    - Russia ☐
    - UK ☐
    - US ☐
    - Other (enter code) ☐

    ____, ____, ____, ____, ____, ____

    - Not specified ☐

16. What was the racial/ethnic population studied?
(Check all that apply)

- Caucasian ☐
- African Ancestry ☐
- Hispanic ☐
- Asian ☐
- Native American ☐
- Eskimo/Inuit ☐
- Other (enter code) ☐
- Not described ☐

17. What was the percent of male participants?
(Enter number or 999)

____ ____ ____ %

18. What was reported for the following questions regarding subjects ages? (Enter number 99 for not reported)

- Mean Age ____ ____
- Median Age ____ ____
- Age Range ____ ____ to ____ ____

19. What were the study's inclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ____, ____ ____

____ ____, ____ ____, ____ ____, ____ ____

20. What were the study's exclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ____, ____ ____

____ ____, ____ ____, ____ ____, ____ ____

21. Was a validated dietary assessment method described?
(CIRCLE ONE)

- Yes 1
- No 2
- Not described 8
- Not applicable 9

22. Was the omega 3 fatty acid content described in the baseline diet?
(CIRCLE ONE)

- Yes (please answer Q23) 1
- No (please SKIP Q23) 2
- Not applicable (not RCT or CCT, SKIP Q23) 9

23. If the omega 3 content was described in the baseline diet, please specify the quantification:

(Example: Fish 8 grams per week, please use codes for source and units.)

Source (code)	Number (Enter #)	Source Unit (code)	Time Unit (code)

Source Units

1. grams	6. tabs
2. oz	7. ml
3. mg	8. other
4. servings	9. ND
5. caps	

Time Units

1. hour	5. year
2. day	6. ND
3. week	
4. month	

Interventions (for all study designs)

24. Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.
For observational studies answer only columns denoted with asterisks (*):

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-Intervention(s) or Co-exposure(s)
1	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
2	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
3	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
4	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
					1.Hour 2.Day 3.Week 4.Month 5.Year 6.BID 9.NA				

21. See instructions on previous page.

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-Intervention(s) or Co-exposure(s)
5	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
6	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
7	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
8	P PY CNTRL CASES					Total O3 ☐ ALA ☐ DHA ☐ EPA ☐ DPA ☐ Not Reported ☐ Not Applicable ☐			
					1.Hour 2.Day 3.Week 4.Month 5.Year 6.BID 9.NA				

24. See instructions on previous page.

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of * treatment	Units *	Co-intervention(s) or Co-exposure(s)
9	p PY CNTRL _____ NENTERING CASES _____ NCOMPLETING					Total O3 ..... ☐ ALA..... ☐ DHA..... ☐ EPA..... ☐ DPA..... ☐ Not Reported. ☐ Not Applicable ☐			
10	p PY CNTRL _____ NENTERING CASES _____ NCOMPLETING					Total O3 ..... ☐ ALA..... ☐ DHA..... ☐ EPA..... ☐ DPA..... ☐ Not Reported. ☐ Not Applicable ☐			
11	p PY CNTRL _____ NENTERING CASES _____ NCOMPLETING					Total O3 ..... ☐ ALA..... ☐ DHA..... ☐ EPA..... ☐ DPA..... ☐ Not Reported. ☐ Not Applicable ☐			
12	p PY CNTRL _____ NENTERING CASES _____ NCOMPLETING					Total O3 ..... ☐ ALA..... ☐ DHA..... ☐ EPA..... ☐ DPA..... ☐ Not Reported. ☐ Not Applicable ☐			
	Enter a number for PY entering and PY completing or enter 999 if not reported. If observational study, circle appropriate unit of measurement: P: Persons PY: Person years CNTRL: Control	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number: 1. g 2. mg 3. ml 4. IU	Enter a number: 1. Hour 2. Day 3. Week 4. Month 5. Year 6. NO 9. NA	Enter a number: 1. Yes 2. No 3. O3 9. NA	Enter a number: 997. Variable 998. NO 999. NA	Enter a number: 1. Hour 2. Day 3. Week 4. Month 5. Year 6. NO	Enter code(s) Maximum number 'digits in a cell is 100

								9 NA	

Case report /Case series/Cohort specific questions

Instructions: For case report, case series, and cohort studies ONLY, please fill out this page (Q25-Q29), otherwise SKIP to Q30.

25. Were case controls identified from any of the following locations:

(CHECK ALL THAT APPLY)

Community .....
Hospital .....
Health care system (non-hospital) .....
Nursing home .....
Not described .....
Not Applicable (cohort studies) .....

26. Was there blinded assessment of the following:

(CIRCLE ONE PER EACH ROW)

	Yes	No	N/A
Eligibility of cases and controls' Or exposed vs. unexposed	1	2	3
Assessment of outcome	1	2	3
Assessment of exposure	1	2	3

27 In the analysis, was any attempt made to adjust for known confounders, not included in matching?

(CIRCLE ONE)

Yes 1
No 2

28 Were cases and controls matched by any of the following characteristics?

(CHECK ALL THAT APPLY)

Age .....
Sex .....
Underlying neurological disease .....
Cognitive function .....
Educational level .....
Other characteristics .....
Not matched .....
Not applicable .....

29. Was ascertainment of cases valid? (CIRCLE ONE)

Yes 1
No 2

Outcomes

30. Please enter the type of outcomes measured. For case series, case report, or cohort enter the outcome that defines the study:

Enter code for each outcome measured	Enter code(s) for each set of adjustments made for each outcome measured (Please separate with commas)		

31. Overall, was a validated method used for ascertainment of clinical outcomes? (CIRCLE ONE)

Yes 1
No 2
Not applicable 9

Evaluation

32. When, relative to the start of the intervention or exposure, were outcomes reported?

(Write the number/code in the appropriate box)

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups		

Units	
1. Hour	5. Year
2. Day	8. ND
3. Week	9. NA
4. Month	997. Variable

33. What was the total duration of the study?

(Number) (Units: use codes from above)

Adverse Events

34. Were any of the following adverse events mentioned? (Check all that apply)

Clinical bleeding ..... ☐
Dermatological ..... ☐
Diarrhea ..... ☐
GI complaint or nausea ..... ☐
Headaches ..... ☐
Withdrawal due to adverse event ..... ☐
Other adverse events ..... ☐
No Adverse events ..... ☐
Not described ..... ☐
Not applicable ..... ☐

For CANCER studies only, answer Q35-37. If not a cancer study then SKIP.

35. Is the state of the immune system described? (CIRCLE ONE)

Yes 1
No 2

36. Are the effects of omega 3 fatty acids on the outcomes of any of the following reported? (Check all that apply)

Cancer surgery ..... ☐
Chemotherapy ..... ☐
Radiation ..... ☐
None of the above ..... ☐

37. Does the study describe genes involved in omega 3 fatty acid transport or metabolism? (CIRCLE ONE)

Yes 1
No 2

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

Appendix C. Evidence Tables

Evidence Table C.1.1 Part A. Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies.*

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease	Applicability
Cohort				**Ascertainment**	**Funding source**
					Quality
Barberger-Gateau, 2002[21]	Sample size (people/person years): 1,416/NR	Duration: 7 years	Inclusion: Age = 68/Normal cognition/Living at home	Disease: Dementia	Applicability: II
PAQUID (Personnes Agées QUID) Study	Age (mean/range): NR/68–99		Exclusion: Dementia	Ascertainment: MMSE; neurological exam	Funding source: Industry and private
	Race: NR				Quality:
	% male: NR				Adjustment for confounders: Y
	# sites: 1				Blinding of exposure/outcome: N
	Location: France				Valid ascertainment of outcome: Y
					Valid ascertainment of exposure: NR
					Exposure before outcome: Y
					Selection bias: N
					Description of withdrawals and dropouts: Y

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease	Applicability
Cohort				Ascertainment	Funding source
					Quality
Kalmijn, 1997[59]	Sample size (people/person years): 818/NR	Duration: 3 years	Inclusion: NR	Disease: cognitive function, normal aging and incidence of dementia	Applicability: II
Zutphen Elderly Study	Age (mean/range): NR/69–89		Exclusion: NR	Ascertainment: Clinical exam; MMSE	Funding source: Government
	Race: NR				Quality:
	% male: 100				Adjustment for confounders: Y
	# sites: 1				Blinding of exposure/outcome: N
	Location: Netherlands				Valid ascertainment of outcome: Y
					Valid ascertainment of exposure: Y
					Exposure before outcome: Y
					Selection bias: N
					Description of withdrawals and dropouts: Y
Kalmijn, 1997[67]	Sample size (people/person years): 5,386/NR	Duration: 2.1 years	Inclusion: Residents of a suburb in Rotterdam, age ≥ 55	Disease: Dementia	Applicability: II
Rotterdam Cohort	Age (mean/range): 67.7/NR		Exclusion: Cambridge Mental Disorders of the Elderly Examination (CAMDEX) score below 80; illogical answers to food pattern questionnaire	Ascertainment: Medical records or medical examination	Funding source: Government
	Race: NR				Quality:
	% male: 41				Adjustment for confounders: Y

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease	Applicability
Cohort				**Ascertainment**	**Funding source**
					Quality
	# sites: 1				Blinding of exposure/outcome: NR
	Location: Netherlands				Valid ascertainment of outcome: Y
					Valid ascertainment of exposure: Y
					Exposure before outcome: Y
					Selection bias: N
					Description of withdrawals and dropouts: Y
Morris, 2003[23]	Sample size (people/person years): 815/NR	Duration: 3.9 years	Inclusion: Normal cognition	Disease: Alzheimer's disease	Applicability: I
Chicago Health and Aging Project	Age (mean/range): 73/NR		Exclusion: NR	Ascertainment: NINCDS criteria, neurological exam	Funding source: Government
	Race: Caucasian and Black				Quality:
	% male: 39				Adjustment for confounders: Y
	# sites: 1				Blinding of exposure/outcome: Y
	Location: U.S.				Valid ascertainment of outcome: Y
					Valid ascertainment of exposure: Y
					Exposure before outcome: Y

Author, Year	Type of Dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect				Applicability
Cohort					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
Cohort									Selection bias: N Description of withdrawals and dropouts: Y

* NR = not reported.

Evidence Table C.1.1 Part B. Evidence table of the effects of omega-3 fatty acids on cognitive function and dementia in cohort studies by category of omega-3 consumption.*

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect				
Cohort					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
FISH									
Barberger-Gateau, 2002[21]	Dementia	1	NR	NR	1.0		1.0		Age, sex, education
PAQUID (Personnes Agées QUID) Study		2	1122	At least once a week	0.66†	(0.47–0.93)	0.73†	(0.52–1.03)	
	Alzheimer's disease	1	NR	NR	1.0		NR		
		2	1122	At least once a week	0.69†	(0.47–1.01)	NR		
			Total 1122						
Kalmijn, 1997[67]	Total dementia	1	1807	≤ 3 g/day	NR		1.0		Age, sex, education, total energy intake.
Rotterdam Study		2	1773	3.0–18.5 g/day	NR		0.8	(0.4–1.4)	
		3	1806	> 18.5 g/day	NR		0.4	(0.2–0.9)	

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect				
Cohort					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
								p = 0.03‡	
	Alzheimer's disease without vascular component	1	1807	≤ 3 g/day	NR		1.0		
		2	1773	3.0–18.5 g/day	NR		0.9	(0.4–1.8)	
		3	1806	> 18.5 g/day	NR		0.3	(0.1–0.9)	
								p = 0.005‡	
	Dementia with a vascular component	1	1807	≤ 3 g/day	NR		1.0		
		2	1773	3.0–18.5 g/day	NR		0.6	(0.2–2.5)	
		3	1806	> 18.5 g/day	NR		0.7	(0.2–2.8)	
			Total 5386					p = 0.39‡	
Morris, 2003[23]	Alzheimer's disease	1	121	never	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
Chicago Health and Aging Project		2	250	1–3 servings/months	0.7	(0.3–1.6)	0.6	(0.3–1.3)	
		3	296	1 serving/ week	0.5	(0.2–1.0)	0.4	(0.2–0.9)	
		4	148	≥ 2 servings/week	0.6	(0.2–0.9)	0.4	(0.2–0.9)	

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect				
Cohort					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
		Total 815				p = 0.18‡		p = 0.07‡	
Omega-3 fatty acids									
Morris, 2003[23]	Alzheimer's disease	1	NR	0.9 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
Chicago Health and Aging Project		2	NR	1.13 g/day	1.1	(0.4–2.9)	1.2	(0.5–3.0)	
		3	NR	1.30 g/day	0.5	(0.2–1.4)	0.6	(0.2–1.7)	
		4	NR	1.49 g/day	0.6	(0.2–1.5)	0.7	(0.3–1.6)	
		5	NR	1.75 g/day	0.3	(0.1–0.7)	0.4	(0.1–0.9)	
		Total 815				p = 0.01‡		p = 0.01‡	
ALA									
Morris, 2003[23]	Alzheimer's disease	1	NR	0.72 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
Chicago Health and Aging Project		2	NR	0.92g/day	1.7	(0.7–3.8)	1.8	(0.8–3.8)	

Author, Year	Type of dementia	Study arm (quartile, quintile or dose group)	Total n	Amount by category	Estimates of effect				
Cohort					Age adjusted RR (95% CI)		Multivariable RR (95% CI)		Multivariable Adjustors
		3	NR	1.06g/day	0.8	(0.4–1.9)	0.8	(0.4–2.0)	
		4	NR	1.23g/day	0.8	(0.4–1.7)	0.9	(0.4–2.0)	
		5	NR	1.46g/day	0.5	(0.2–1.1)	0.7	(0.3–1.6)	
			Total 815			p = 0.01‡		p = 0.10‡	
DHA									
Morris, 2003[23]	Alzheimer's disease	1	NR	0.03 g/day	1.0		1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
Chicago Health and Aging Project		2	NR	0.05 g/day	0.8	(0.3–2.1)	0.8	(0.3–2.1)	
		3	NR	0.06 g/day	0.4	(0.1–1.1)	0.4	(0.1–1.0)	
		4	NR	0.07 g/day	0.3	(0.1–0.9)	0.2	(0.1–0.8)	
		5	NR	0.10 g/day	0.4	(0.2–1.1)	0.3	(0.1–0.9)	
			Total 815			p = 0.05‡		p = 0.02‡	
EPA									

First Author, Year	Study Type Characteristics	Study Design (quintile dose group)	Duration	Eligibility criteria	Amount by category	Concurrent Disease Condition	Medication	Arm	Interventions Dosage/Duration
Cohort						**Age adjusted RR (95% CI)**	**Multivariable RR (95% CI)**		**Multivariable Adjustors**
Morris, 2003[23]	Alzheimer's disease	1		NR	0.0 g/day	1.0	1.0		Age, sex, race, education, vitamin E intake, other fat intake, cardiovascular disease, APO-ε4 status.
Chicago Health and Aging Project		2		NR	0.0.g/day	NR§	NR§	NR§	NR§
		3		NR	0.01 g/day	1.0	(0.4–2.4)	1.1	(0.4–2.8)
		4		NR	0.02 g/day	0.5	(0.2–1.2)	0.5	(0.2–1.2)
		5		NR	0.03 g/day	0.9	(0.4–2.1)	0.9	(0.4–2.3)
			Total 815				p = 0.40‡		p = 0.40‡

* NR = not reported, g = grams;

† hazards ratio;

‡ age and sex adjusted; test for trend;

§ Authors report that 40% of participants had 0 g/day of intake.

Evidence Table C.2.1 Part A. Evidence table of the effects of omega-3 fatty acids on the treatment of dementia in RCTs.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Terano, 1994[24]	Sample size (people/person years): 20/NR	Design: RCT	Inclusion: Other dementia	NR	1	Intervention: Standard hospital diet
	Age (mean/range): 83/NR	Duration: 12 months	Exclusion: NR			Dosage: NR

First Author, Year Cohort	Study Characteristics Results	Duration Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Disease Ascertainment	Applicability Quality Funding Source
	Range: NR % male: NR # sites: 1 Location: Japan				2	Intervention: DHA Dosage: 4.3 grams/day for 12 months

* NR = not reported

Evidence Table C.2.1 Part B. Evidence table of the effects of omega-3 fatty acids on the treatment of dementia in RCTs.*

First Author, Year	Outcomes					Quality
	Results					Applicability Funding Source
Terano, 1994[24]	Study arms	Results				Quality
		Before	After 3 months	After 6 months	After 12 months	Jadad: 1
	Mean scores of HDS-R					Concealment of Allocation: NR
	Standard nursing home diet	16.3	16.7	16.7	15.3	**Applicability:** II-B
	Standard nursing home diet PLUS DHA 4.3 grams/day	17.2	20.6†	19.9†	20.2	**Funding Source:** NR
	Mean scores of MMSE					
	Standard nursing home diet	19.7	19.4	19.6†	19.1	
	Standard nursing home diet PLUS DHA 4.3 grams/day	20.1	21.3	22.2	21.9	

* NR = not reported, HDS-R = Hasegawa's Dementia rating scale; MMSE = Mini Mental Status Exam.

† $p < 0.05$ with paired t-test.

Evidence Table C.3.1 Part A. Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

First Author, Year Cohort	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability Funding source Quality

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability
Cohort					**Funding source**
					Quality
Chen, 2003[34]	Study Design: Cohort	Duration: Variable years	Inclusion: NR	Disease: Parkinson's	Applicability: II
Health Professionals Follow-up Study Cohort and The Nurses' Health Study Cohort	Sample size (people/person years): 135,894/NR		Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake	Ascertainment: neurological exam	Funding source: Government and private (non-industry)
	Age (mean/range): NR/30–75				Quality:
	Race: NR				Adjustment for confounders: Y
	% male: 35				Blinding of exposure/outcome: Y
	# sites: 1				Valid ascertainment of outcome: Y
	Location: US				Valid ascertainment of exposure: Y
					Exposure before outcome: Y
					Selection bias: N
					Description of withdrawals and dropouts: NR
Ghadirian, 1998[43]	Study Design: Case-Control	Duration: NR	Inclusion: Multiple sclerosis	Disease: MS	Applicability: II
	Sample size (people/person years): 399/NR		Exclusion: NR	Ascertainment: Neurological exam, Kurtzke/EDSS	Funding source: NR
	Age (mean/range): NR/NR				Quality:

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability
Cohort					**Funding source**
					Quality
	Race: NR				Adjustment for confounders: Y
	% male: 31				Blinding of exposure/outcome: Y
	# sites: 1				Valid ascertainment of outcome: Y
	Location: Canada				Valid ascertainment of exposure: Y
					Exposure before outcome: Y
					Groups comparable: Y
					Selection bias: N
					Description of withdrawals and dropouts: Y
Petridou, 1998[60]	Stdy Design: Case-Control	Duration: NR	Inclusion: NR	Disease: CP	Applicability: II
	Sample size (people/person years): 337/NR		Exclusion: NR	Ascertainment: Clinical exam; registry	Funding source: Government and private
	Age (mean/range): 5/4–8				Quality:
	Race: NR				Adjustment of confounders: Y
	% male: 53				Blinding of exposure/outcome:
	# sites: 1				Valid ascertainment of outcome: Y
	Location: Greece				Valid ascertainment of exposure: Y

First Author, Year	Study Characteristics	Duration	Eligibility criteria	Disease Ascertainment	Applicability
Cohort					**Funding source**
					Quality
					Exposure before outcome: Y
					Groups comparable: Y
					Selection bias: Y
					Description of withdrawals and dropouts: Y
Zhang, 2000[61]	Study Design: Cohort	Duration: 14 years	Inclusion: NR	Disease: MS	Applicability: II
Nurses' Health Study Cohort	Sample size (people/person years): 187,811/NR		Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake	Ascertainment: neurological exam; Poser criteria	Funding source: Government
	Age (mean/range): NR/25–55				Quality:
	Race: NR				Adjustment of confounders: Y
	% male: NR				Blinding of exposure/outcome: Y
	# sites: 1				Valid ascertainment of outcome: Y
	Location: US				Valid ascertainment of exposure: Y
					Exposure before outcome: Y
					Selection bias: N
					Description of withdrawals and dropouts: Y

* NR = not reported

Evidence Table C.3.1 Part B. Evidence table of the effects of omega-3 fatty acids on incidence of neurological diseases in cohort and case control studies.*

Author, Year Cohort Disease		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect Multivariable RR (95% CI)		Multivariable Adjustors, Matching parameters
Fish							
Zhang, 2000[61]		1	81	< 1/week	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
The Nurses' Health Study I and II		2	77	1–2.9/week	1.0	(0.8–1.4)	*Matching:* NA
Multiple Sclerosis		3	37	3–4.9/week	0.9	(0.6–1.3) p = 0.79‡	
Ghadirian, 1998,[43]	Men	Control	64		1.0		*Multivariable adjustors:* Total energy, body mass index
Multiple sclerosis		Case	61		1.08	(0.84–1.40)	*Matching:* Age, sex, phone number
	Women	Control	138		1.0		
		Case	136		0.83	(0.69–1.00)	
	All	Control	202		1.0		
		Case	197		0.91	(0.78–1.05)	
Petridou, 1998,[60]		Control	166	1/week	1.0		*Multivariable adjustors:* 'Core' variables§ plus total energy intake, body mass index
Cerebral palsy		Case	58	1/week	0.63	(0.37–1.08)	*Matching:* Age, neighborhood or age, physician
Omega-3 fat from fish							

Author, Year		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect		
Cohort Disease					**Multivariable RR (95% CI)**		**Multivariable Adjustors, Matching parameters**
Chen, 2003[34]	Men	1	NR	0.03 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
Health Professional Follow-up Study and The Nurses' Health Study, Parkinson's Disease		2	NR	0.07% of energy	0.84	(0.52–1.37)	*Matching:* NA
		3	NR	0.1% of energy	1.08	(0.69–1.69)	
		4	NR	0.2% of energy	0.88	(0.55–1.40)	
		5	NR	0.3 % of energy	0.99	(0.63–1.55)	
			Total 47,331	p = 0.9‡			
	Women	1	NR	0.03 % of energy	1.0		
		2	NR	0.05 % of energy	0.70	(0.41–1.19)	
		3	NR	0.08 % of energy	0.76	(0.45–1.29)	
		4	NR	0.1% of energy	0.75	(0.45–1.26)	
		5	NR	0.2 % of energy	0.90	(0.55–1.47)	
			Total 88,563			p = 0.9‡	
	Pooled men and women	1	NR	NR	1.0		
		2	NR	NR	0.77	(0.54–1.11)	

Author, Year		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect		
Cohort Disease					Multivariable RR (95% CI)		Multivariable Adjustors, Matching parameters
		3	NR	NR	0.93	(0.66–1.31)	
		4	NR	NR	0.82	(0.58–1.16)	
		5	NR	NR	0.94	(0.68–1.32)	
		Total 135,894				p = 0.9‡	
ALA							
Chen, 2003[34]	Men	1	NR	0.05 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
Health Professional Follow-up Study and The Nurses' Health Study, Parkinson's Disease		2	NR	0.06% of energy	0.54	(0.34–0.87)	*Matching*: NA
		3	NR	0.08% of energy	0.75	(0.49–1.15)	
		4	NR	0.09% of energy	0.88	(0.58–1.32)	
		5	NR	0.1 % of energy	0.69	(0.45–1.07)	
		Total 47,331				p = 0.4‡	
	Women	1	NR	0.04 % of energy	1.0		
		2	NR	0.06 % of energy	0.83	(0.51–1.34)	
		3	NR	0.07 % of energy	0.71	(0.43–1.17)	
		4	NR	0.09% of energy	0.68	(0.41–1.13)	
		5	NR	0.1 % of energy	0.60	(0.35–1.01)	

Author, Year		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect		
Cohort Disease					**Multivariable RR (95% CI)**		**Multivariable Adjustors, Matching parameters**
		Total 88,563				p = 0.04‡	
	Pooled men and women	1	NR	NR	1.0		
		2	NR	NR	0.67	(0.47–0.93)	
		3	NR	NR	0.73	(0.53–1.01)	
		4	NR	NR	0.79	(0.57–1.09)	
		5	NR	NR	0.65	(0.46–0.91)	
		Total 135,894				p = 0.05‡	
EPA							
Chen, 2003[34]	Men	1	NR	0.009 % of energy	1.0		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption
Health Professional Follow-up Study and The Nurses' Health Study, Parkinson's Disease		2	NR	0.02 % of energy	0.77	(0.48–1.25)	
		3	NR	0.04 % of energy	0.88	(0.56–1.39)	
		4	NR	0.06 % of energy	0.92	(0.59–1.44)	
		5	NR	0.1 % of energy	0.91	(0.59–1.42)	
		Total 47,331				p = 0.9‡	

Author, Year		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect		
Cohort Disease					Multivariable RR (95% CI)		Multivariable Adjustors, Matching parameters
	Women	1	NR	0.007 % of energy	1.0		
		2	NR	0.01 % of energy	0.67	(0.39–1.16)	
		3	NR	0.02 % of energy	0.80	(0.48–1.34)	
		4	NR	0.04 % of energy	0.74	(0.44–1.24)	
		5	NR	0.07 % of energy	0.91	(0.56–1.49)	
		Total 88,563				p = 0.8‡	
	Pooled men and women	1	NR	NR	1.0		
		2	NR	NR	0.73	(0.51–1.04)	
		3	NR	NR	0.84	(0.60–1.19)	
		4	NR	NR	0.84	(0.60–1.18)	
		5	NR	NR	0.91	(0.66–1.27)	
		Total 135,894				p = 0.9‡	
DHA							
Chen, 2003[34]	Men	1	NR	0.02 % of energy	1		*Multivariable adjustors:* Age, smoking (cigarettes/day), energy intake (quintiles), alcohol consumption

Author, Year		Study arm (quartile: quintile: dose group; case or control)	n†	Amount by category	Estimates of effect	
Cohort Disease					**Multivariable RR (95% CI)**	**Multivariable Adjustors, Matching parameters**
Health Professional Follow-up Study and The Nurses' Health Study Parkinson's Disease		2	NR	0.05 % of energy	0.79 (0.49–1.28)	
		3	NR	0.07 % of energy	1.05 (0.67–1.64)	
		4	NR	0.1 % of energy	0.90 (0.57–1.42)	
		5	NR	0.2 % of energy	0.92 (0.58–1.44)	
		Total 47,331			p = 0.9‡	
	Women	1	NR	0.02 % of energy	1	
		2	NR	0.04 % of energy	0.62 (0.36–1.07)	
		3	NR	0.06 % of energy	0.65 (0.38–1.09)	
		4	NR	0.08 % of energy	0.81 (0.49–1.32)	
		5	NR	0.1 % of energy	0.76 (0.46–1.26)	
		Total 88,563			p = 0.8‡	
	Pooled men and women	1	NR	NR	1	
		2	NR	NR	0.71 (0.49–1.02)	
		3	NR	NR	0.86 (0.61–1.21)	
		4	NR	NR	0.86 (0.61–1.20)	

First Author, Year Author, Year	Study Characteristics	Study Design Duration	Study Eligibility criteria (quartile: quintile: dose group; case or control)	n†	Amount by category	Concurrent Disease Condition Medication	Estimates of effect Dosage/Duration
Cohort Disease						Multivariable RR (95% CI)	Multivariable Adjustors, Matching parameters
			5	NR	NR	0.84 (0.60–1.18)	
				Total 135,894			p = 0.8‡

* NR = Not Reported;

>† Number of people included in analysis;

‡ test for trend.

§ Core variables = Age of child, sex, maternal age at menarche, maternal age at delivery, maternal chronic disease, previous spontaneous abortion, persistent vomiting during index pregnancy, multiple pregnancy, number of obstetric visits, timing of membrane rupture, use of general anesthesia, mode of delivery, abnormal placenta, head circumference, evident congenital malformation, place of deliver, use of Fe during pregnancy, intention al physical exercise during pregnancy, painless delivery classes.

Evidence Table C.4.1 Part A. Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Concurrent Disease Condition Medication	Arm	Interventions Dosage/Duration
Bates, 1989[40]	Sample size (people/person years): 312/NR	Design: RCT	Inclusion: MS defined by specific criteria/Acute relapsing/Kurtzke Disability Scale=6	Vitamin E, N6 polyunsaturated fat, Dodecylgallate	1	Intervention: Olive oil
	Age (mean/range): 34/16–35	Duration: 24 months	Exclusion: Chronic disease history			Dosage: 10 grams/day for 24 months
	Race: NR				2	Intervention: Max EPA
	% male: 32					Dosage: 10 grams/day for 24 months
	# sites: 3					
	Location: UK					
Cendrowski, 1986[62]	Sample size (people/person years): 12/NR	Design: Single arm open label trial	Inclusion: MS defined by specific criteria	None	1	Intervention: w-3 and w-6 polyunsaturated fatty acids (MaxEPA)

First Author, Year	Study Characteristics / Results	Study Design / Duration	Eligibility criteria	Concurrent Disease / Condition / Medication	Quality / Applicability / Funding Source	Interventions Dosage/Duration
	Age (mean/range): NR/33–64 Race: NR % male: 50 # sites: 1 Location: UK	Duration: Variable months	Exclusion: NR			Dosage: 20–30 ml/day
Nordvik, 2000[63]	Sample size (people/person years): 16/NR Age (mean/range): 32/22–37 Race: NR % male: 35 # sites: 1 Location: Norway	Design: Single arm open label trial Duration: 2 years	Inclusion: Relapsing/remitting MS/Stable neurological status Exclusion: Immunosuppressive medications use/Vitamins use/Fish supplements/Steroids use/Change in diet	None	1	Intervention: Long-chain marine fatty acids and vitamins Dosage: 0.9 g/day

* NR = not reported.

Evidence Table C.4.1 Part B. Evidence table of the effects of omega-3 fatty acids on the progression of multiple sclerosis in clinical trials.*

First Author, Year	Outcomes / Results	Quality / Applicability / Funding Source
Bates, 1989[40]	Outcome 1: Kurtzke Disability Scale scores Arm 1 = Olive oil 10 grams/day for 24 months Arm 2 =Max EPA 10 grams/day for 24 months Reported testing: p = 0.07 (not statistically significant) for comparison between groups Outcome 2: Duration and number of relapses	**Quality** Jadad: 3 Concealment of Allocation: NR **Applicability:** II-B **Funding Source:** Private

First Author, Year	Outcomes	Quality
	Results	**Applicability**
		Funding Source
	Arm 1 = Olive oil 10 grams/day for 24 months	
	Arm 2 =Max EPA 10 grams/day for 24 months	
	Reported testing: Not statistically significant for comparison between groups; statistics not reported	
	Outcome 3: Fatty acid analysis	
	Arm 1 = Olive oil 10 grams/day for 24 months	
	Arm 2 =Max EPA 10 grams/day for 24 months	
	Reported testing: Significant increases in EPA and DHA in arm 2 subjects in comparison with controls (arm 1) but point estimates not reported.	
Cendrowski, 1986[62]	Outcome 1:Mean EDSS Scores†	**Quality**
	Arm 1: MaxEPA (4..2 g/day EPA; 2.8 g/day DHA)	Comparison groups: None
	Reported testing: p<0.05 significant for reduction on EDSS	Blinding: NR
	Outcome 2: Mean Progression Index	Description of withdrawals/dropouts: NR
	Arm 1: MaxEPA (4..2 g/day EPA; 2.8 g/day DHA)	**Applicability:** II-B
	Reported testing: p<0.05 significant for improvement on index of disease progression	**Funding Source:** NR
Nordvik, 2000[63]	Outcome 1:Mean EDSS Scores†	**Quality**
	Arm 1: Fish oil supplement (0.4 g/day EPA; 05 g/day DHA)	Comparison groups: None
	Reported testing: p<0.05 significant for reduction on EDSS	Blinding: NR
		Description of withdrawals/dropouts: NR
		Applicability: II-B
		Funding Source: Government and Private

* NR = not reported.

† EDSS = Expanded Disability Status Scale.

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MacLean CH, Issa AM, Newberry SJ, et al. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. (Evidence Reports/Technology Assessments, No. 114.)

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Listing of Excluded Studies

Rejected Search Unsuccessful (n = 5)

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Rejected Duplicate (n = 1)

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Bookshelf ID: NBK37657

DECLARATION OF CAROL L. HENRICKS, M.D.

I, Carol L. Henricks, M.D., hereby state and declare as follows:

1. I am a licensed physician specializing in Neurology. Brain science has been a focus of my education and training. My *Curriculum Vitae* is attached.

2. In 1991, I received my M.D. degree from Hahnemann University School of Medicine. Thereafter, I performed my Neurology Residency at Hahnemann University Hospital, where I served as Chief Resident in Neurology. Following my residency, I performed a Fellowship in Clinical Neurophysiology at the University of Michigan. After that, I performed a second Fellowship in Behavioral Neurology and Memory Disorders at the University of Arizona.

3. After completing my second Fellowship, I went into private practice as a specialist in Neurology. I have been in private practice for the past 18 years.

4. I participated in several research projects involving memory function. I was a research assistant in memory studies at Yale University and the University of Pittsburgh Learning Research and Development Center, and I conducted research on the clinical neurophysiology of learning and memory during medical school.

5. In early April, 2016, I spoke to Sharon Harris, an attorney at the Zimmerman Law Offices, in connection with settlement discussions that Sharon and other attorneys at her firm were having relative to a case against CVS. We talked about docosahexaenoic acid (DHA), which is an omega-3 fatty acid that is a primary structural component of the human brain and cerebral cortex, among other things.

6. It is well-established in medicine that DHA promotes normal brain development and cognitive function. Taking dietary DHA supplements is associated with the maintenance of normal brain and cognitive functions, such as memory and learning abilities.

EXHIBIT B

7. Sharon asked whether the phrase "pure DHA memory support" would be supported by the relationship between DHA and brain health. I told Sharon my opinion is that taking dietary DHA supplements supports brain development, cognitive function, and memory. My opinion was based on my training, education, research and experience, and my review of reliable medical and scientific studies.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge, information and belief, and that this declaration was executed on September 28, 2016.

Carol Henricks, M.D.

Curriculum Vitae

Carol L Henricks, MD

Current Employment: Private Practice: self-employed as a subspecialist.
Behavioral Neurology, Epilepsy, Sleep Disorders,
Traumatic Brain Injury and Hyperbaric Medicine.

NorthStar Neurology, PC and NorthStar Hyperbaric

Fellowship: University of Arizona, Tucson AZ 7/97-6/98
Behavioral Neurology and Memory Disorders.
(Dr. Geoff Ahern and Dr. Steve Rapcsak)

Fellowship: University of Michigan, Ann Arbor, MI 7/95-6/97
Clinical Neurophysiology: Epilepsy, Sleep Disorders.

Chief Resident: Neurology: July 1994-June 1995.

Residency: Hahnemann University Hospital, Philadelphia PA
7/92-6/95 Neurology Residency.

Internship: Hahnemann University Hospital, Philadelphia PA
7/91-6/92 Internal Medicine.

Diplomat of the National Board of Medical Examiners 1992. Board Eligible:
American Board of Psychiatry and Neurology.

Medical Education: Hahnemann University School of Medicine
Philadelphia PA. 1987-1991. MD June 1, 1991.

Undergraduate: Washington and Jefferson College, Washington PA
BA in Psychology 1981.

Other Education: Graduate Courses in Engineering at Carnegie Mellon University, Graduate Courses in Neuropsychology at University of Bridgeport, Advanced Math classes (Calculus III, IV) University of Pittsburgh, Graduate Courses at Fuller Seminary.

Research Experience includes:

NorthStar Hyperbaric facility designated as a treatment center for the NBIRR study treating veterans with Traumatic Brain Injury. Fall 2009. Study has been completed and data is being analyzed.

Clinical Drug trials of novel anticonvulsants. University of Michigan Ann Arbor, Michigan. 7/95-6/97.

Neurophysiology Research. Hahnemann University, Philadelphia Pennsylvania: Clinical Neurophysiology of learning and memory as part of Graduate studies during medical school, but PhD was not completed. I surgically implanted deep brain recording electrodes into rats to correlate the firing patterns with new learning. 9/87-5/89.

Memory research. Yale University, New Haven Connecticut. Research assistant in studies using healthy college students to understand how healthy memory functions learning new material. 9/84 to 8/ 87

Memory research at University of Pittsburgh Learning Research and Development Center. University of Pittsburgh, Pittsburgh Pennsylvania. Educational and Psychological research assistant: studies on how people learn, understand and remember physics principles. 9/81 to 6/84

Other :

Clinical Supervisor at the St. Andrews Clinic for Crippled Children. Nogales, Arizona. Volunteer work managing problems in children with crippling neurological conditions. (1998 – 2007)

Staff Neurologist at Arizona Training Program. Neurological consultant to all residents. Residents have suffered devastating neurological conditions since childhood. 2003 – 2013.

Staff Neurologist at Tucson Heart Hospital on call 24 – 7 for consults. 2001 – November 2012: hospital closed.

"Hyperbaric Oxygen Therapy in recovery from Spinal Cord Injury" International Hyperbaric Medical Association Meeting (IHMA), Long Beach, California August, 2008.

"Ani: A case study" (Late recovery from multiple early childhood injuries using HBOT). IHMA Meeting, Long Beach, California August, 2010.

"Recovery from Chronic Traumatic Encephalopathy with HBOT as demonstrated by Brain MRI with DTI". IHMA Meeting, Long Beach, California August, 2012.

Other presentations include Grand Rounds, presentations to local medical societies and interested groups. Member of the Pima County Medical Society Public Health Committee. Written articles have appeared in the Sombrero, Tucson Natural Awakenings and the AAPS journal.

Medical Director of Healing Arizona Veterans, a non – profit organization which educates, informs and provides treatment for TBI injured military veterans of the current conflict.

After working in a private neurology practice in Yuma, AZ for 6 months after finishing my second Fellowship in 1998, I started my own neurology practice in Tucson in 1999.

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